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Original Communications

THE ERYTHROCYTE SEDIMENTATION RATE IN HUMAN SUBJECTS RECEIVING DICUMAROL

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DICUMAROL depresses the production of prothrombin which belongs to the globulin fraction of the blood. Since the sedimentation rate is closely related to the plasma concentration of fibrinogen and globulin,[1] the problem arises whether the erythrocyte sedimentation rate is altered in the course of Dicumarol therapy. Contradictory opinions have been expressed.

Allen and his associates[2] originally stated that the sedimentation rate was almost routinely increased in their patients receiving Dicumarol, but subsequently concluded that the drug had little or no effect on the sedimentation rate.[3] Others noted that the sedimentation rate was increased to such an extent by the drug that it no longer served as an index of healing of a myocardial infarct[4] or that Dicumarol medication made this test less dependable clinically.[5,6] Wright and Prandoni,[7] on the other hand, concluded that Dicumarol had no significant effect on the sedimentation rate in thromboembolic diseases. Quick[8] observed no appreciable change in the sedimentation rates of two dogs under Dicumarol therapy. Nalefski and LeRoy[9] noted that the sedimentation rates of dogs following experimental coronary occlusion showed no consistent pattern and the Dicumarol appeared to have no influence upon this. Bruzelius[10] and Cosgriff[11] obtained similar results in man.

In view of these conflicting reports it was deemed advisable to undertake the present study. Normal subjects were chosen since it is not possible to evaluate accurately the effect of Dicumarol in pathologic states where the underlying disease itself may cause variations in the erythrocyte sedimentation rate.

METHOD

Ten, healthy, ambulatory volunteers, ranging from 22 to 26 years of age, were selected after careful examination. Following control determinations the

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subjects ingested Dicumarol in quantities designed to elevate their undiluted plasma prothrombin time to the accepted therapeutic range of 25 to 35 seconds (Table I) as determined by the Quick one-stage method[12] with 13 seconds representing 100 per cent. Fasting blood samples collected in vials containing ammonium and potassium oxalate crystals were used for the determination of the sedimentation rates, hemoglobin, erythrocyte and leucocyte counts. The sedimentation rates were tested by the Westergren method[13] with values up to 20 mm. per hour being considered normal. A photoelectric colorimeter was used for the hemoglobin determinations. The total serum proteins, albumin, and globulin were determined by the Weichselbaum method.[14] Urines were examined routinely for hematuria and urobilinogen. All determinations were done shortly after the specimens were taken. Daily oral temperatures remained normal throughout the period of the experiment.

TABLE I. MILLIGRAMS OF DICUMAROL GIVEN ORALLY

DAY	SUBJECT 1	SUBJECT 2	SUBJECT 3	SUBJECT 4	SUBJECT 5	SUBJECT 6	SUBJECT 7	SUBJECT 8	SUBJECT 9	SUBJECT 10
1	300	300	300	300	300	300	300	300	300	300
2	150	150	200	200	200	200	—	200	200	200
3	150	100	100	100	100	—	400	100	100	—†
4	50	50	—	—	—	—*	—	200	200	—
5	50	50	—	—	—	—	200	100	100	—
6	—	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	200	—	—	—
Totals	700	650	600	600	600	500	1100	900	900	500

*72 mg. of synthetic vitamin K administered intravenously.
†36 mg. of synthetic vitamin K given intravenously.

RESULTS

Therapeutic prothrombin time levels were obtained in 9 of the 10 subjects. No constant, significant changes in their erythrocyte sedimentation rates were observed which could be attributed to the administration of Dicumarol (Table II). The changes in the sedimentation rate of Subject 4 were attributed to dental work performed on the second day of the experiment. No important changes were detected in the other laboratory determinations.

Subject 6 began menstruating 11 days prematurely after taking a total of 500 mg. of Dicumarol in three days. Although her prothrombin time was only 23.6 seconds, she was given 72 mg. of synthetic vitamin K intravenously. Subject 10 received 36 mg. of synthetic vitamin K intravenously when his prothrombin time reached 43.8 seconds after a total dose of 500 mg. of Dicumarol.

CONCLUSION

1. Therapeutic doses of Dicumarol do not significantly influence the erythrocyte sedimentation rate in normal, ambulatory subjects.

TABLE II. PROTHROMBIN TIMES AND ERYTHROCYTE SEDIMENTATION RATES OF THE TEN SUBJECTS RECEIVING DICUMAROL

	SUBJECT 1			SUBJECT 2			SUBJECT 3			SUBJECT 4			SUBJECT 5			SUBJECT 6			SUBJECT 7			SUBJECT 8			SUBJECT 9			SUBJECT 10		
DAY	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.	P.T.	PER CENT	S.R.
1	15.0	68	5.0	14.5	90	4.0	16.1	55	0.0	15.1	66	18.5	14.2	98	4.0	16.7	49	16.0	18.2	39	10.0	11.6	100	4.0	12.1	100	6.0	13.5	100	1.0
2	15.5	60	3.5	15.0	68	3.0	13.5	100	2.5	15.4	61	22.0	17.2	46	4.0	15.1	66	21.0	13.9	99	9.0	12.7	100	5.0	14.4	98	7.0	16.3	49	0.0
3	14.5	90	3.0	22.7	78	5.0	21.7	30.5	5.0	19.6	32	30.0	21.5	31	6.0	18.9	38	19.0	13.7	99	11.0	25.6	23	7.0	24.8	23	5.0	43.8	8	1.0
4	22.7	28	5.0	28.1	19	3.0	24.8	24	2.5	27.3	19.5	23.5	29.4	16.5	2.0	23.6	26	15.0	17.7	43	24.2	24.2	25	5.0	24.6	24	9.0	29.0	17	1.0
5	30.5	16	4.0	31.0	15.5	3.5	25.6	23	4.0	31.0	15.5	21.5	29.4	16.5	5.0	21.7	31	20.0	18.6	39	8.0	25.0	23	5.0	27.0	20	5.0	23.1	27	1.0
6							23.9	25	3.0	27.1	20	21.0	24.2	25.5	5.0				20.6	31	12.0	36.9	13	4.0	36.2	12	9.0	30.2	16	1.0
7	28.2	18	4.0	33.5	15	4.0																								
8	20.2	32	9.0			5.0													22.9	28	14.0	24.2	25	10.0	23.4	26	11.0	16.0	56	1.0
9	22.4	28.5	5.0	32.5	15	5.0				22.5	28	22.0	15.1	66	2.0							24.1	26	11.5	23.0	27	10.0			
10																			31.4	15.5	11.0									
11	17.0	47	4.0	26.2	22	3.0													26.4	22	11.0	16.8	45	4.0	16.2	54	8.0			
12																														
13																			21.8	30	4.0									
14																														
15				14.5	90	6.0																								
16																			14.0	98	12.0									

P.T., prothrombin time in seconds; per cent, prothrombin present; S.R., erythrocyte sedimentation rate in mm. per hour.

2. Therefore, the clinical value of the sedimentation rate in patients receiving Dicumarol therapeutically remains unaltered.

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SIGNIFICANCE OF THE REFERENCE OF ANGINAL PAIN TO THE RIGHT OR LEFT SIDE OF THE BODY

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ANGINAL pain is felt substernally and often radiates to the sides of the neck and the arms as far as the fingers. This reference may occur on both sides, though it is usually much more marked on, or even confined to, the left. Rather infrequently it is restricted to the right. Radiation to the left arm alone occurs about twenty-five times more often than to the right arm alone, but radiation to both arms is frequent, being about one-fourth as common as that to the left arm alone. The more severe the pain or distress in the left arm, the more likely it is to be felt also in the right arm.[10] This article is an attempt to attach significance to the side of reference of the pain.

Each of the paired structures in the body is supplied with nerve fibers from the corresponding side of the cord. The same seems to be true of each half of a structure which in the embryo is originally in the midline. The gut and trachea are such structures and Jackson and Jackson[5] showed that electrodal stimulation of the mucosa of the esophagus on one side caused muscular contraction on the same side of the body only. Stimuli in the midline caused contractions on both sides. This shows that one half of the esophagus is connected to the corresponding side of the nervous system only. In a case recently observed by the writer bronchoscopy revealed a marked inflammation with vasodilatation strictly confined to the mucosa of the right half of the whole length of the trachea and sharply limited in the saggital plane. This suggests that the vasodilator nerve fibers from one side of the trachea are derived from that side of the body and nervous system. In the embryo the fundus of the stomach is originally a left-sided structure, lying to the left of the midline celiac axis, and the prepyloric region, pylorus, and duodenum are right-sided, lying to the right of the midline superior mesenteric artery. They receive their nerve supply in the fourth week of human fetal development. It has been found that referred pain from the fundus of the stomach is felt in the left side and is abolished by blocking of the left dorsal sixth to eighth nerve roots, while referred pain from the prepyloric region, pylorus, or duodenum is felt on the right side and is abolished by blocking of the right dorsal seventh and eighth nerve roots. It is evident that the nerve supply of various viscera is established very early in fetal life and depends on the side of the body on which the organ forms, and that each half of an originally midline structure receives its nerve supply from the corresponding side of the nervous system.

Developmentally the mediastinum and diaphragm evolve from the tissues of the septum transversum and into this structure grow the liver and gall bladder anlage. That part of the gut which forms the stomach originally lies in the septum. The pericardium lies within the mediastinum and on the diaphragm. It follows that the right or left side of the mediastinum is supplied by right or left-sided nerve fibers respectively and that this nerve supply is closely related to that of the stomach, gall bladder, and diaphragm. Right-sided anginal pain from mediastinal disease must, therefore, mean disease of the right side of the mediastinum, while the reverse is true of left-sided pain. This is borne out by the chief reference of pain in the patient described in a previous paper by the author.[12] In this patient a para-esophageal hernia occurred into the left side of the mediastinum and the pain was chiefly referred to the left arm. In the patient described in the following report an aneurysmal projection of the right side of the aorta, with no evidence of extension in any other direction or of cardiac disease, led to anginal pain restricted to the right side.

CASE 1.—The patient, a 60-year-old ship's engineer, attended Out-Patients Department, Royal Cancer Hospital on June 24, 1947, under the care of Dr. P. E. T. Hancock. He had been subject to a winter cough with some slight mucoid expectoration for a number of years. For two to three months prior to attendance dyspnea had appeared on exertion. Nine weeks prior to attendance, within the course of a few days he had developed increasingly severe pain around the right side of the upper chest radiating to the right shoulder, arm, and elbow. The pain was strictly localized to the right side. Its severity increased within the course of a few days and for thirty to forty hours became intense, after which it eased, though it had never left him since that time. The pain was increased by exertion and by use of the right arm and eased by rest and keeping the arm still. In the last week or so his voice had become husky and the cough more troublesome.

On examination the patient's general condition was found to be good. There was no dyspnea at rest. The face was somewhat suffused, with fullness of the transverse cervical vein on the right. No glandular enlargement or tracheal displacement or tug were felt. The pupils were normal. The apex beat was just inside the nipple line in the left fifth intercostal space; the heart sounds were normal and no murmurs were heard. An area of dullness extended laterally from the right side of the upper sternum outward for a variable distance and over this pulsation was visible and palpable, but no thrill could be felt. The pulses were equal on the two sides. Blood pressure in the right arm was 110/70, in the left 140/80. Breath sounds were weak and some rhonchi were heard over the upper anterior portion of the chest on the right side. No abnormalities were detected in other systems. The Wassermann and Kahn reactions were strongly positive. X-ray examination and screening of the chest showed a large pulsating mass extending from the right hilum forwards and to the right. It arose from the right side of the ascending aorta, causing some slight collapse in the middle and upper zones of the right lung. The heart was not enlarged. The electrocardiogram showed no abnormality.

NERVE SUPPLY OF THE HEART

The heart is supplied by nerve fibers from the cardiac plexuses by two main groups. The fibers of one pass behind the transverse sinus of the pericardium in the venous mesocardium to the atria, where they form a large atrial plexus, and those of the other pass in front of the sinus in the arterial mesocardium, where they follow the coronary vessels to the ventricles (Perman[8]). The heart is supplied by both vagus and sympathetic nerves through fibers coming from both

sides of the nervous system and also by posterior root fibers on both sides. The nerves transmitting the impulses causing angina pass from the heart into the first to fourth dorsal (fifth?) and eighth cervical posterior nerve roots on both sides and are of unmyelinated type. These roots also supply fibers to the tissues of the mediastinum.

EARLY STAGES OF DEVELOPMENT OF THE HEART

The following account is largely that of Arey[1] and of Keith.[6] In the vertebrate embryo, including that of man, the first change after the formation of the gastrula is the appearance of the neural folds. Even before these begin to fuse, the cells of the neural crest, which form the spinal and cranial nerve ganglia, begin to differentiate off on either side and their processes rapidly grow out to supply the tissues on the corresponding side of the embryo. On both sides some cells migrate to form the cells and fibers of the autonomic system and the cells of the adrenal medulla. These outgrowths commence before fusion of the neural folds, which begins in the region that eventually becomes the hindbrain and from here extends in both directions. Immediately afterward, at the 2.5-mm. stage or fourth week in the human embryo, the formation of the somites starts, also in the region of the hindbrain.

The first-formed blood vessels are paired and appear when somite formation is beginning (2.5 mm.). They consist of paired vitello-umbilical veins entering caudally the paired unfused heart tubes, which lead into the paired ventral and dorsal aortas (Fig. 1). By the six-somite stage the paired heart tubes have fused into a single heart and the ventral aortas have also joined. In the embryo possessing fifteen to twenty-three somites, paired pre- and postcardinal veins enter the paired common cardinal veins (ducts of Cuvier) and the dorsal aortas have begun to fuse into a single dorsal aorta. The heart tube grows and becomes bent and twisted and certain structural changes take place in it, whereby its auricular (atrial) segment is brought into contact with its terminal or aortic segment. Early in the fourth week of development the primitive heart has the appearance shown in Fig. 2. The sinus venosus or first chamber receives the common cardinal veins (ducts of Cuvier) on either side. It leads into the second or atrial chamber and this into the ventricle, which projects ventrally and caudally and at its most ventral portion turns sharply forwards and dorsally to form the bulbus cordis leading to the truncus arteriosus and ventral aorta. In fish and in the human embryo the sinus serves as a reservoir during systole of the atrium, the right and left venous valves at the junction of the sinus and atrium preventing the regurgitation of blood during atrial systole. The right and left venous valves meet to form an inferior fornix below and above a superior fornix in front of the superior caval opening above. The opening of the sinus into the atrium is a midline structure (Fig. 4).

Nerve fibers start to invade the heart toward the end of the fourth week.[11] This occurs from the neural crests on both sides by way of the venous mesocardium to the atrial end and through the arterial mesocardium to the bulbar end of the

heart. The right sides of the primitive chambers are supplied by fibers from the right side of the nervous system and the left side by those from the left.

As the heart develops further there appear on the atrial segment of the cardiac tube right and left diverticula. The sinus venosus becomes absorbed into the right diverticulum. The venous valves become atrophic, the sinus venosus remaining as that part of the right atria between their remnants. Owing to the great shortening of the ventral part of the atrial segment the inferior fornix of the venous valve becomes fused with the posterior endocardial cushion.

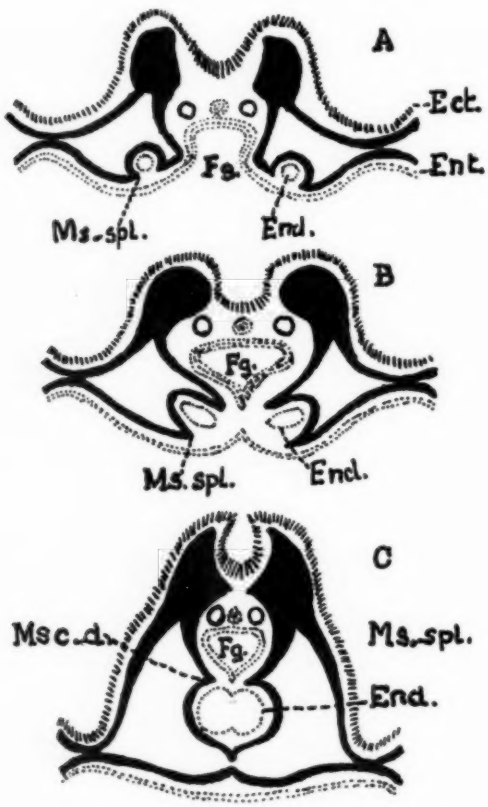

Fig. 1.—Diagram to illustrate the origin of the heart in higher vertebrates. *Ect.*, ectoderm; *End.*, endothelial tubes; *Ent.*, entoderm; *Fg.*, foregut; *Msc. d.*, dorsal mesocardium; *Ms. spl.*, sphanchnic mesoderm (epi- and myocardium). (Modified from Arey after Strahl and Carius.)

The left horn of the sinus remains as the coronary sinus, into which flows the oblique vein of Marshall, the remnant of the left duct of Cuvier. The right diverticulum of the primitive atrium forms the appendix of the adult heart and all that part of the right atrium which is furnished with musculi pectinati. The sulcus terminalis of the adult heart marks the line between the primitive atrium and sinus. In the adult heart that part of the right atrium formed by the sinus

venosus is indicated by the entrance of those vessels which were originally tributaries of the sinus, namely, the superior vena cava (right duct of Cuvier), inferior vena cava, and the oblique vein of Marshall (left duct of Cuvier) opening into the left horn of the sinus venosus, which becomes the coronary sinus. The right venous valve becomes: the Thebesian valve (valve of coronary sinus), the Eustachian valve (valve of inferior vena cava), and the taenia terminalis. The left venous valve becomes a fretted membrane on the septal margin of the inferior caval orifice and the band of musculature accompanying this remnant (Fig. 3).

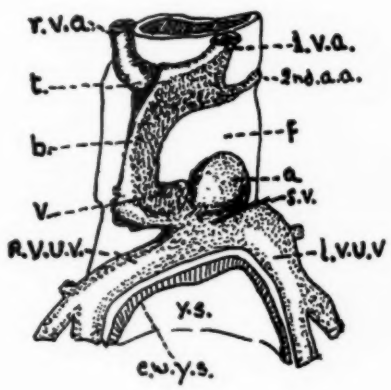

Fig. 2

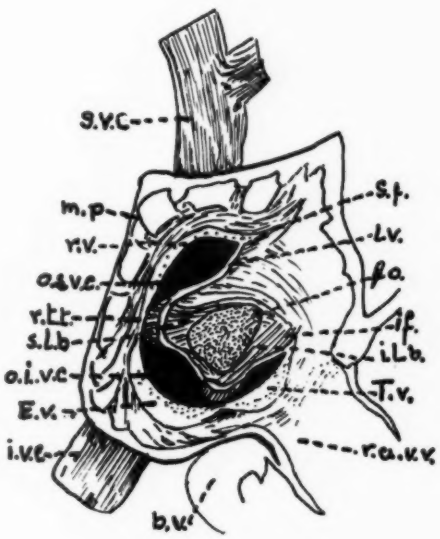

Fig. 3

Fig. 2.—The parts of the human heart as seen on their ventral aspect, early in the fourth week of gestation. Only the endocardial lining is represented. *r.v.a.*, right ventral aorta; *t.*, truncus arteriosus; *b.*, bulbus cordis; *v.*, ventricle; *r.v.u.v.*, right vitello-umbilical vein; *l.v.a.*, left ventral aorta; *2nd. a.a.*, second aortic arch; *f.*, foregut; *a.*, auricle; *s.v.*, sinus venosus; *l.v.u.v.*, left vitello-umbilical vein; *y.s.*, yolk sac; *c.w.y.s.*, cut wall of yolk sac. (Redrawn from Keith after Veit and Esch.)

Fig. 3.—Diagram of the right atrium thrown open to show the position and relation of the right and left venous valves and the manner in which they are broken up by the superior and inferior limbic bands. *s.v.c.*, superior vena cava; *m.p.*, musculi pectinati; *r.v.*, remains of right venous valve; *o.s.v.c.*, opening of superior vena cava; *r.t.t.*, right taenia terminalis; *s.l.b.*, superior limbic band; *o.i.v.c.*, opening of inferior vena cava; *E.v.*, Eustachian valve; *i.v.c.*, inferior vena cava; *b.v.*, base of ventricle; *s.f.*, superior fornix; *L.v.*, remains of left venous valve; *f.o.*, fossa ovalis; *i.f.*, inferior fornix; *i.L.b.*, inferior limbic band; *T.v.*, Thebesian valve; *r.a.v.v.*, right atrioventricular valve. (Redrawn after Keith.)

The musculature of the sinus venosus of fishes is made up of peculiar small fibers rich in nuclei and in nerve supply and, more than all the musculature of the heart, has the power of automatic rhythmical contraction. In mammalian hearts these fibers persist only at the sulcus terminalis marking the junction of the sinus and atrium on the right side and in the wall of the coronary sinus. Elsewhere the muscle of the sinus appears to be replaced by that of the atria.

The area of primitive fibers of the right side of the sinus persisting in the sulcus terminalis lies just in front of the superior vena cava and forms the sinoatrial node. This is supplied chiefly by the right vagus and other right-sided nerve fibers. The opening of the sinus venosus of the embryo reaches the posterior endocardial cushion just below the orifice of the coronary sinus, in the wall of which the special muscle fibers of the sinus venosus persist. In this region is found a node of peculiar muscular tissue. This is the atrioventricular node, which is supplied chiefly by the left vagus and other fibers from the left side of the cord. This suggests that the tissues of the node represent part of the original left sinus musculature and are analogous with the sinoatrial node, which is part of the original right sinus musculature.

In the Dipnoan fishes, in which the swim-bladder serves as a lung, the pulmonary vein passes along the left wall of the sinus venosus to open in the left side of the atrium near the base of the left venous valve. In the human embryo, as in the Dipnoi, the pulmonary vein opens by a single orifice in the left diverticulum of the primitive atrium. This vein is formed by the junction of the right and left veins, each of which is made up of two tributaries. Gradually more and more of the single vein is absorbed into the auricle, so that first a right and left pulmonary vein open separately into the atrium and later each of the two main tributaries of these veins also enters the left side of the chamber. The absorbed part of the pulmonary vein and its tributaries eventually becomes the vestibule of the left atrium. In the fully developed heart the left atrium is thus formed by the left primitive atrium, which merely forms the appendix of the chamber, and by the vestibule, which is marked off from the rest of the atrium by a prominent muscular band.

The septum primum appears at the beginning of the sixth week as a crescentic fold on the roof of the primitive atrium (Fig. 4). Its lower margin is attached to both endocardial cushions, and the three structures eventually fuse. In mammals and birds the upper part of the septum breaks down forming the foramen ovale. The septum secundum then forms by an inflexion of muscle from the roof of the atrium to the right of the septum primum (Fig. 4). Its site corresponds roughly with the left venous valve.

Thus, in the atria of the adult human heart the sinoatrial node and everything to the right of the remnants of the right venous valve are right-sided structures and are supplied by right-sided nerves, including the vagus passing to the sinoatrial node. Everything to the left of the remnants of the left venous valve, including the A-V node, interatrial septum, and left atrium are left-sided structures and are supplied by left-sided nerves, including the vagus.

In the A-V canal, posterior and anterior endocardial cushions grow from the dorsal and ventral walls toward one another and fuse, thus dividing the canal into two. The inferior fornix of the fused venous valves of the sinus venosus, a midline structure, fuses below with the posterior cushion. Thus, the septum dividing the right and left A-V canals is a midline structure. The interventricular septum, which divides the two ventricles, is continuous with the fused posterior and anterior endocardial cushions and the anterior and posterior cushions of

the bulbus cordis. Hence, unlike the interatrial septum, the interventricular septum is a midline structure. The right ventricle and the orifice of the pulmonary artery are thus right-sided structures and the left ventricle and aortic orifice are left-sided.

To conclude, on embryological grounds it appears that the interatrial septum, left atrium and left ventricle, the commencement of the aorta, the oblique vein of Marshall, and the coronary sinus are left-sided structures. The remainder of the right atrium, the right ventricle, and the origin of the pulmonary artery are right-sided. The interventricular septum is a midline structure. The right and left-sided structures are supplied by nerves from the corresponding side of the nervous system.

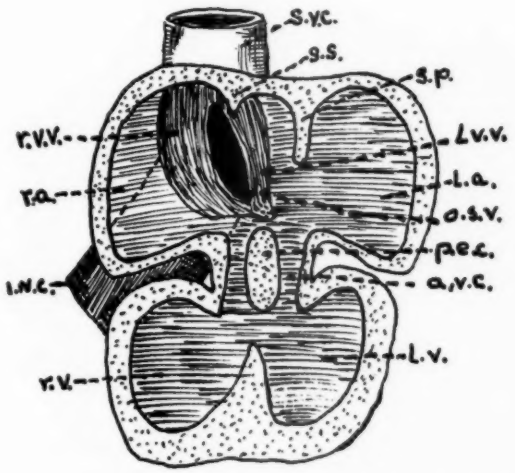

Fig. 4.—Section of the heart of a six-week human embryo showing the right and left venous valves, which guard the entrance of the sinus venosus into the primitive atrium. *r.v.v.*, right venous valve; *r.a.*, right atrium; *i.v.c.*, inferior vena cava; *r.v.*, right ventricle; *s.v.c.*, superior vena cava; *s.s.*, septum secundum; *s.p.*, septum primum; *l.v.v.*, left venous valve; *l.a.*, left auricle; *o.s.v.*, open sinus venosus; *p.e.c.*, posterior endocardial cushion; *a.v.c.*, atrioventricular canal; *l.v.*, left ventricle; *i.v.s.*, interventricular septum. (Redrawn from Keith after His.)

EVOLUTION OF THE VERTEBRATE HEART

Light is thrown on the laterality of the chambers of the heart by a study of its evolution in vertebrates. Primarily the heart consists of sinus venosus, atrium, ventricle, and truncus arteriosus, all lying in the midline and with undivided chambers. The common cardinal veins enter the sinus venosus and the aortas leave the truncus arteriosus. The sinoatrial opening is a midline structure. In the Dipnoan fish and amphibia a portion of the left side of the atrium becomes divided off by the septum, which is obviously left-sided (Fig. 5). It forms the left atrium and receives the pulmonary vein. The common ventricle is divided by a midline structure, which is at first incomplete, as in lower reptiles. In mammals and birds the heart chambers and septa correspond to those in reptiles, though the previous midline situation becomes lost in the adult. The same

conclusions as to the laterality of the heart structures must be drawn from the facts of comparative anatomy as from those of embryology, namely, that the left auricle and interatrial septum and left ventricle are left-sided and the rest of the right atrium and right ventricle are right-sided structures.

CLINICAL AND PATHOLOGICAL EVIDENCE BEARING ON THE QUESTION OF RIGHT AND LEFT-SIDED STRUCTURES IN THE HEART

In the rare conditions of total hemihypertrophy and hemiatrophy all the structures on one side of the body are either hypertrophied or atrophied respectively. Significantly the blood vessels and the heart take part in these changes. In patients with hemihypertrophy, the blood vessels, especially their medial and intimal coats, are much thickened on the affected side and the corresponding

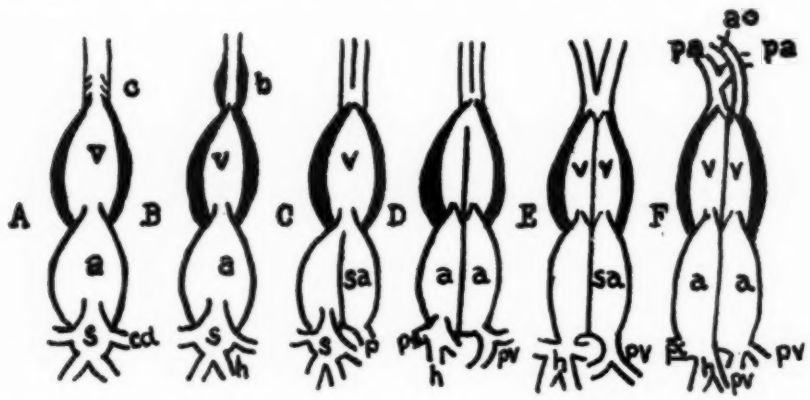

Fig. 5.—Different stages in the differentiation of the parts of the heart, ventral view. *A*, elasmobranch; *B*, teleosts; *C*, amphibia; *D*, lower reptiles; *E*, alligator; *F*, birds and mammals. *a*, atrium; *ao*, aorta; *b*, bulbus arteriosus; *c*, conus; *cd*, Cuverian duct; *h*, hepatic veins; *pa*, pulmonary artery; *pc*, pre- and postcaval veins; *pv*, pulmonary vein; *s*, sinus venosus; *sa*, septum atriorum; *v*, ventricles. (Redrawn from Kingsley's "Comparative Anatomy of Vertebrates".)

atrium and ventricle are also involved (Hornstein,[4] Arnheim,[2] Cassirer and Hirschfeld.[3]) The reverse is true in patients with total hemiatrophy. Such abnormalities may be either congenital in nature or acquired. Not infrequently lesions of the bulb of the nervous system have been present and their appearance in acquired cases has been related causally to the onset of the unilateral changes. An example is a patient described by Leri,[7] in whom hemiatrophy followed a fracture of the skull and the appearance of the signs of a lesion of one side of the medulla. These facts again show that the chambers of the right and left sides of the heart and the blood vessels of the two sides are right and left structures respectively and are correspondingly supplied by right and left-sided nerves.

CONCLUSION

On embryological, phylogenetic, and clinical grounds, therefore, it must be concluded that the left and right sides of the heart are supplied by nerves from the left and right sides of the nervous system respectively. The interatrial

septum and A-V node are left-sided structures. The impulses concerned in causing anginal pain arise on the coronary vessels or perhaps in the myocardium and are conducted by unmyelinated fibers passing into the first to fourth (fifth?) dorsal and eighth cervical posterior nerve roots on both sides. In the same nerve roots run fibers supplying the mediastinal structures. If the appropriate left posterior nerve roots are injected with alcohol, anginal pain is abolished on the left side only (White and Smithwick[9]). It follows that impulses concerned with left-sided pain are transmitted by the fibers passing into the left posterior nerve roots and those with right-sided pain by fibers in the right roots. Since the nerves from the right side of the heart supply the blood vessels of the right chambers and the left nerves those of the left chambers, it follows that right-sided pain means dysfunction of the right chambers and left-sided of the left chambers and interatrial septum.

Other clinical observations confirm these deductions. In cases of coronary thrombosis or angina occurring in subjects with a heart on the left side of the body the vascular changes and infarction involve chiefly the left ventricle and atrium and sometimes also the right. The pain is usually referred either partially or entirely to the left side and is practically never restricted to the right side. This suggests that greater involvement of the chambers of the left side of the heart is related to the occurrence of greater pain on the left side. In cases of isolated dextrocardia a coronary thrombosis would chiefly involve the right ventricular wall. In the following patient with dextrocardia accompanied by angina the pain was usually referred entirely to the right, but occasionally spread slightly to the left side. This suggests that pain from disease of the chambers of the right side of the heart is referred by way of the right nerve roots.

CASE 2.—A 56-year-old laborer attended the Out-Patients Department, Hounslow Hospital on March 3, 1947. He had been well until some four weeks previously, when he was seized at work with severe substernal pain, which radiated to the right arm and right side of the neck only. It was accompanied by severe sweating, vomiting, and pallor. He was taken home by ambulance and remained in bed for several days. The pain and vomiting eased after about twelve hours. Against his doctor's advice he had insisted on getting up five days later. Since then he had experienced substernal pain, usually radiating only to the right arm as far as the elbow, but occasionally passing to the left shoulder. The pain came on after he walked about 50 yards and was eased if he stood still. It was followed by a burning soreness of the skin on the inner side of the upper right arm. It never occurred at rest. No complaint was made of dyspnea or edema of the ankles.

The patient was a heavily built, bald man, weighing 199 pounds. The skin was pale, but the mucosae were of good color and not cyanosed. There were no signs of congestive heart failure. The pulse was regular. There was a considerable degree of arteriosclerosis present, both in the radial and retinal vessels. The apex beat was situated in the right sixth intercostal space 4½ inches from the midline. The heart sounds were loud and the aortic second sound accentuated, but no murmurs were present. The blood pressure was 180/110. The lungs were clear and there was no clubbing of the fingers. The urine contained a trace of albumin. Radiographs and screening of the chest showed the presence of dextrocardia, but the gas in the fundus of the stomach was seen to be on the left side and the diaphragm on this side was lower than on the right. The right ventricle showed a moderate degree of enlargement. The aorta was left-sided. No hilar congestion was present. A barium meal revealed that there was no inversion of the abdominal viscera. The electrocardiogram showed a complete inversion of the tracing in Lead I, in which the T wave was absent. Both T_2 and T_3 were inverted. In Lead II the R wave was low and the S wave increased in amplitude.

The occurrence of angina in a small proportion of patients with mitral stenosis is well known and is usually attributed to accompanying coronary artery disease, but this is not always present.[10] In the following patient with mitral stenosis anginal pain of effort was strictly localized to the right side. A diagnosis of Lutembacher's disease was thought probable.

CASE 3.—The patient, a 48-year-old ex-nurse, attended Hounslow Hospital on June 6, 1947. While nursing in World War I at the age of 19 years she developed pneumonia and three years later, while on duty, she fainted and was found to have "heart trouble." At the age of 31 years she became increasingly dyspneic, her ankles began to swell, and she had severe palpitations. She was found to be suffering from auricular fibrillation and was given digitalis. At the age of 38 years, in addition to her other symptoms, she developed severe substernal pain extending to the right arm and not affecting the left side at all. The pain only appeared on exertion and was eased by rest. She began to suffer from increasingly severe symptoms of bronchitis particularly in the winter with occasional hemoptyses and later nocturnal asthmatic attacks. For the last six years she had been unable to sleep except in the sitting position.

The patient had orthopnea, mitral facies, and severe cyanosis of the lips, nose, ears, and fingers. There was no fullness of the cervical veins, enlargement of liver, or edema of ankles. Auricular fibrillation was noted. The blood pressure was 120/100. An apex beat was felt in the left fifth intercostal space 4 inches from the midline. There was marked pulsation in the pulmonary area. A loud systolic murmur was heard at the apex and another apparently distinct murmur in the tricuspid area. No presystolic murmur was audible. First and second heart sounds were clearly heard at the apex, but no first sound was audible at the base, although the second sound at the pulmonary area was very loud. There was no murmur in the pulmonary area. Expansion of the chest was poor. Many rhonchi were heard in all areas, but no râles or signs of edema of the lung bases were made out. Radiographs and screening of the chest showed no enlargement of the left ventricle, atrium, or aorta, even when barium was swallowed. There was, however, great enlargement of the pulmonary artery, right ventricle, and right atrium, but no "hilar dance" was seen and the enlargement of the pulmonary vessels did not seem sufficient for a definite diagnosis of Lutembacher's disease. An electrocardiogram confirmed the auricular fibrillation, the P complexes being absent and T_2 and T_3 waves inverted. There was a marked right ventricular preponderance.

In this patient the extreme dyspnea and cyanosis, enlargement of the pulmonary artery, right ventricle, and atrium, and marked right ventricular preponderance in the electrocardiogram indicate severe pulmonary hypertension with a strain chiefly on the right ventricle. It is significant that the pain was confined to the right side suggesting that it was related to activity of the right ventricle.

SUMMARY

(1) Embryological, phylogenetic, and clinical evidence is brought forward to show that the right side of the mediastinum, the chambers of the right side of the heart, and the sinoatrial node are right-sided structures and disease affecting these structures may cause right-sided reference of anginal pain. The left side of the mediastinum, left chambers of the heart, pulmonary veins, interatrial septum, and atrioventricular node are left-sided structures. In them disease may cause left-sided anginal pain.

(2) Three case histories of right-sided anginal pain are presented and discussed.

I would like to thank Dr. P. E. Thompson Hancock for his kind permission to publish details of Case 1.

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TETRAETHYLAMMONIUM CHLORIDE IN THE TREATMENT OF ANGINA PECTORIS

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ACHESON and Moe[1] in 1945 showed that the tetraethylammonium ion (TEA) improved work capacity of the dog heart and that this improvement varied from slight in those subjects with little evidence of failure to dramatic in those with more severe failure. Loewi[2] demonstrated in isolated frogs' hearts that tetraethylammonium antagonizes the depressant action of vagomimetic quaternary bases (acetylcholine and tetramethylammonium), of tertiary bases (pilocarpine and arecoline), and of potassium. In the isolated frog's heart all these compounds act at a site peripheral to the nerves. Further studies showed that, in intact animals, tetraethylammonium blocks transmission of sympathetic and parasympathetic nerve impulses at the ganglia.[3,4] The response of the heart rate to the usual doses of tetraethylammonium in intact animals is probably dependent on whether sympathetic cardioaccelerator tone, or vagal cardioinhibitory tone predominates at the time of administration of tetraethylammonium.[3]

In man, a moderate increase in heart rate is the usual result of tetraethylammonium therapy, though at times the rate may remain the same or be slowed.[5] Ballistocardiographic studies showed a temporary increase in cardiac output of about 20 per cent following administration of tetraethylammonium to normal and hypertensive subjects.[6] A significant fall in venous pressure occurs in normal subjects and patients with elevated venous pressure.[7]

Early in its clinical use, tetraethylammonium was found to afford dramatic relief from pain in angina pectoris and coronary occlusion. Despite this, it was thought that the sudden decrease in blood pressure might lead to myocardial ischemia and that, therefore, tetraethylammonium might not be safe for use in treatment of these patients.[7,8]

In 1925, Mandl[9] reported sixteen patients with angina pectoris whom he treated by paravertebral injection of the sympathetic ganglia with 0.5 per cent Novocain. The patients obtained relief of pain and an increase in the amount of work which they could do. This improvement persisted for a much longer time than would have been expected from the duration of Novocain action. This suggested that other temporary ganglionic blocking agents might give similar results.

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In January, 1947, we first began the treatment of a patient who had unusually severe and intractable angina pectoris with tetraethylammonium chloride (TEAC).* Symptomatic improvement was striking and we were encouraged to treat other patients. Twenty-eight patients suffering from angina pectoris have now been treated with tetraethylammonium chloride; eighteen have been on this therapy for from six to twenty months.

METHOD OF EVALUATION OF RESULTS

Before beginning treatment with tetraethylammonium chloride, all patients were stabilized on accepted methods of treatment, such as phenobarbital, nitroglycerin, and, whenever indicated, digitalis and ammonium chloride. Each patient was evaluated for several months on this regime. Tetraethylammonium chloride was then begun as an additional measure.

All patients were without financial means and most had undesirable environmental conditions with many mental and emotional problems. We did not treat them from this viewpoint during this study. The difficulty of getting them to and from the clinic was often sufficient to cause an increase in the number of anginal attacks. The benefits of tetraethylammonium chloride therapy had to overcome the deleterious effects of the exertion and excitement involved in coming to the clinic for treatments.

Because of the electrocardiographic changes which already existed, most patients were not suitable candidates for Master's exercise test or the anoxemia test. Therefore they were evaluated by the number of attacks of anginal pain per week and by exercise tolerance in terms of everyday tasks. Exercise tolerance was recorded in terms of the number of successive blocks walked without stopping before a pain was induced, and the number of stairsteps climbed. Although this method is subject to variations caused by many factors, it permits clinically adequate assessment of general trends in the patient's condition over a period of time.

DOSE AND METHOD OF ADMINISTRATION

The optimal dose of tetraethylammonium chloride for treatment of angina pectoris varied greatly from patient to patient. Responsiveness to the drug was usually increased by severe heart disease, old age, arteriosclerosis, and some forms of hypertension. If the dose was too large, patients with one or more of these factors were more likely to experience greater hypotension and other unpleasant side effects. The optimal dose was determined for each patient by beginning with small intravenous doses (50 or 100 mg.) and working up to the optimal dose.

The patient is told at the time of administration that he may experience a transitory slight metallic taste, followed by a tingling or cold sensation in hands and feet. He is then asked to tell when each of these occurs and the strength of the sensation. Blood pressure readings are taken at two and five minutes. If

*Tetraethylammonium chloride (TEAC) was furnished as "Etamon" by Dr. E. C. Vonder Heide of Parke, Davis & Company, Detroit, Mich.

he does not develop tingling, or if it develops in his hands and not his feet, the dose is probably too small and should be increased, provided the blood pressure has not fallen too precipitously. (Moderate falls in blood pressure are well tolerated and the fall is very temporary.) If a larger dose is necessary, it can usually be given ten or fifteen minutes after the first dose. The smallest dose which will give a pronounced tingling sensation in the feet seems to be the optimal dose.

Tetraethylammonium chloride is never given except with the patient lying down. When the optimal dose is found, blood pressure is taken every five minutes after the injection until it has risen to normal range. This is judged as the amount of time that a patient should remain in the supine position after treatment, and gives a rough estimate for the time that he must remain recumbent after future treatments. After this period has elapsed, the patient is allowed to sit up, and, if he is not dizzy, he may stand up. If he feels dizzy, he should lie down for another fifteen minutes and then try again. Using these precautions, we have encountered only a few minor unpleasant side reactions, and no serious reactions, and no toxicity. Early in the series, we had one instance of momentary syncope in a 71-year-old man who stood up too soon.

When doses were too large, several patients became slightly nauseated, either immediately, or on the way home. Several experienced dizziness and lightheadedness for periods up to twelve hours after treatment. These reactions probably represented postural hypotension. Further treatment with smaller doses did not produce unpleasant effects.

When an inadequate dose was given, using sensory stimuli as an indicator, the patient often did not get as good symptomatic improvement of angina as on subsequent occasions when he received a larger dose.

Once the patient's dose and the length of time during which he will have to lie down afterward are determined, treatment may be administered on subsequent visits without the repeated blood pressure determinations, provided the patient has had no major change in cardiac status. Occasionally a patient will fail to get a full sensory stimulus from a previously effective dose, and it will be necessary to repeat the dose with an increase of 50 milligrams. On the other hand, it may be found that, after several treatments, the dose can be decreased slightly without loss in effectiveness. These minor variations are thought to be due to changes in the amount of adrenin which the patient liberates at the time of treatment.[10]

Frequency of treatments was governed by the duration of symptomatic relief and practicability. In general, therapy was given about once every one or two weeks. For the most severe angina pectoris, it was given twice a week until the patient improved sufficiently to decrease the frequency of visits. Occasionally during very severe periods, patients were hospitalized and treatment given every one or two days. Some patients who were on weekly treatments noted a return of pain after three or four days and it was considered that treatment twice a week would be more beneficial, but it was usually impractical for them to be seen that often.

RESULTS

The length of time these twenty-eight patients were treated with tetraethylammonium chloride was: 18 to 20 months, two patients; 15 to 18 months, one; 12 to 15 months, three; 9 to 12 months, six; 6 to 9 months, six; 3 to 6 months, six; and 1 to 3 months, four patients. This does not include the control period for evaluation which preceded the special therapy for each patient. Most patients had very severe heart disease with unmistakable clinical and electrocardiographic evidence of marked coronary insufficiency (Tables I-VI). Over 70 per cent had been either decompensated at sometime or had a myocardial infarction previous to this study. All but two were over 50 years of age and 65 per cent were over 60 (Table VII).

In this series twenty-five of the twenty-eight patients showed definite improvement during treatment. In some, this was noted immediately, whereas others did not show improvement until they had been treated twice a week for several weeks. Of those who improved, 65 per cent showed a significant decrease in anginal pains, and 60 per cent showed a noticeable increase in exercise tolerance (Tables I to V).

Most of the classifications, as arranged according to apparent severity of the disease, showed similar results, except for the group with previous infarction and the group with previous infarction and previous decompensation. Those composing these groups showed, in general, a poorer response than the others. However, no apparent harmful effects, were seen with many doses of tetraethylammonium chloride in these patients with very severe heart disease.

There was not much difference in the response of the various age groups. Two patients over 80 years of age were treated without apparent harmful effects. Response of the other older age groups was surprising and brings up many interesting questions as to the possible mechanisms of action of tetraethylammonium chloride in these patients.

One interesting result was relief of persistent substernal, epigastric, and precordial burning, "hurting," and aching pains and soreness which had not been previously relieved by many nitroglycerin tablets. This was noted in eight patients with angina in whom continuous pain had been present from a few hours up to several weeks. Two other patients, who, after an acute infarction, had almost steady aching and soreness for three and four months, respectively, were relieved, though they continued to have some angina of effort. These pains, like the pain in an acute anginal attack, were relieved within two to five minutes after intravenous administration of tetraethylammonium chloride. Nine of these ten patients had definite signs of coronary insufficiency, and five of them had had previous infarctions. They fall into the group which Freedberg, Blumgart, and associates[11] call "coronary failure." Intravenous calcium gluconate or nicotinic acid in doses sufficient to give a definite sensation, administered before tetraethylammonium chloride in five of the ten patients, gave relief in only one.

Of ten patients whose electrocardiograms were followed carefully for nine months or more, seven showed no change, two showed T-wave improvement (one of these returned to normal), and one became worse.

TABLE I. RESPONSE TO TEAC OF PATIENTS WITH NO ELECTROCARDIOGRAPHIC CHANGES AND NO PREVIOUS DECOMPENSATION

PATIENT	AGE	SEX	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		WEEKS TREATED
			BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
F. S.	50	M	10	2–5	2 caused pain	8 did not cause pain	20 caused pain	20 did not cause pain	18
S. F.	83	F	3–4 Also precordial "hurting" most of the time.	0–1 No "hurting"	½-2 caused pain	4 did not cause pain			30

TABLE II. RESPONSE TO TEAC OF PATIENTS WITH ELECTROCARDIOGRAPHIC CHANGES BUT NO PREVIOUS DECOMPENSATION

PATIENT	AGE	SEX	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		WEEKS TREATED
			BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
M. M.	69	F	3	2	3 caused pain	10 did not cause pain	5 caused pain	17 did not cause pain	4
L. S.	51	M	30	0–1	1½ caused pain	10 did not cause pain	20 caused pain	20 did not cause pain	60
J. W.	71	M	12–25	2–3	2 caused pain	6 caused pain	20 caused pain	40 caused pain	55
P. S.	77	M	5–7 Moderate	1–2 Mild	10-20 caused pain	20 did not cause pain	30-60 caused pain	30 did not cause pain	12
N. D.	64	F	1–2 Moderate	0–1 Mild	½ caused pain	2-3 did not cause pain	7 caused pain	14 did not cause pain	33
A. F.	50	F	32	19 Milder	2 caused pain	5 caused pain	10 caused pain	15 did not cause pain	12

TABLE III. RESPONSE TO TEAC OF PATIENTS WITH ELECTROCARDIOGRAPHIC CHANGES AND PREVIOUS DECOMPENSATION

PATIENT	AGE	SEX	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		WEEKS TREATED
			BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
J. P.	78	M	7–14	3–4	3 caused pain	9 did not cause pain			28
A. P.	58	M	2–4	0–1	Pain not brought on except by hard work More hard work after treatment				39
N. S.	60	M	170	10–14	½ caused pain	1 caused pain	2 caused pain	12 caused pain	80
P. F.*	72	M	7–22	5	½ caused pain	18 did not cause pain	5 caused pain	13 did not cause pain	36
F. T.	69	M	3–9	0–4	4 caused pain	20 caused pain	12 caused pain	22 did not cause pain	26
M. C.	63	F	14–18 Also has periods of steady, severe, aching pain which are relieved immediately by TEAC	0–4	Only one leg and prosthesis limits amount of exercise at all times				48

*Died with bronchopneumonia after 5 weeks of placebos.

TABLE IV. RESPONSE TO TEAC OF PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

PATIENT	AGE	SEX	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		WEEKS TREATED
			BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
T. C.	75	M	12–25	3–4	7-12 caused pains	10 did not cause pain	30 did not cause pain	30 did not cause pain	46
S. S.	69	F	12–15	0–5	6-14 caused pain	6-12 did not cause pain	54 caused pain	54 did not cause pain	55
R. G.	69	F	24–26	2–7	½ caused pain	3-5 caused pain	1 caused pain	18 did not cause pain	70
J. C.	62	M	28–42	2–16	½ caused pain	6-20 caused pain	20 caused pain	20-60 caused pain	84
L. C.	54	M	6–7	0–4	No change—counted as one of 3 failures, because results are somewhat equivocal				47
W. J.	51	M	15–20	0–2	2-3 caused pain	10 did not cause pain	10-20 caused pain	60 did not cause pain	44
L. J.	71	F	Dull "hurting" substernal pain most of the time since infarction (9 months)	Temporary relief for 1-3 days	Results questionable and hard to evaluate due to many psychic factors—Patient seemed slightly better symptomatically, but decompensated once during period treated.—Counted as one of the 3 failures				35
M. S.	42	M	Steady, dull, aching precordial pains for 3 weeks (and most of the time after infarction — 3 months), also many anginal pains	No steady pains. Occasional pain on exertion	Good increase in exercise tolerance, but blocks and steps not measured				9

TABLE V. RESPONSE TO TEAC OF PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION AND PREVIOUS DECOMPENSATION

PATIENT	AGE	SEX	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		WEEKS TREATED
			BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
C. H.	69	M	4	0-2	3 caused pain	4-10 caused pain			13
M. H.	68	M	4 Moderately severe	3 Very mild	4-10 caused pain	4-10 caused pain	10 did not cause pain	20-40 did not cause pain	49
K. R.	57	F	21-28	0-5 But has had several episodes of severe pain	1 caused pain	1-4 caused pain	20 caused pain	20 caused pain	20
C. C.*	85	M	2	2-4	5 caused pain	5-10 caused pain	60 did not cause pain	40 did not cause pain	10
G. N.†	54	F	21	0	½ caused pain	1-2 caused shortness of breath but no pain			8
S. D.	36	M	35 Severe	1 Moderate	0	2	0	20	12

*Patient admitted, ten days after his last clinic visit, with acute myocardial infarct. He became uremic and died 4 days later. Counted as one of the 3 failures.

†Patient stopped attending clinic for 5 weeks and returned with auricular flutter. She refused hospitalization and treatment. We were told by another patient that she died two weeks later at home.

TABLE VI. AVERAGE RESPONSE TO TEAC AS CLASSIFIED BY DISEASE PICTURE

DISEASE PICTURE	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED		PER CENT IMPROVED
	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	
Normal Electrocardiogram and No Previous Decompensation 2 patients	7	3	2 caused pain	6 did not cause pain			100
Electrocardiographic Changes But No Previous Decompensation 6 patients	15	4	4 caused pain	9 did not cause pain	18 caused pain	28 did not cause pain	100
Electrocardiographic Changes and Previous Decompensation 6 patients	37	4	2 caused pain	12 caused pain	6 caused pain	15 did not cause pain	100
Previous Infarction 8 patients	19	4	5 caused pain	9 caused pain	24 caused pain	40 did not cause pain	75
Previous Infarction and Previous Decompensation 6 patients	15	2	2 caused pain	4 caused pain	25 caused pain	30 caused pain	80

In four patients in whom we have obtained a significant electrocardiographic change during an anginal attack, the tracing has reverted to its original appearance two to four minutes after the administration of tetraethylammonium chloride and maintained this configuration (Figs. 1-4). One of these patients (Fig. 4) had been having continuous pain for three days, and had taken thirty glyceryl trinitrate tablets without relief. The other three patients had their pain for only short periods of time.

TABLE VII. AVERAGE RESPONSE TO TEAC AS CLASSIFIED BY AGE

AGE	AVERAGE NUMBER OF PAINS PER WEEK		AVERAGE NUMBER OF BLOCKS WALKED		AVERAGE NUMBER OF STAIRSTEPS CLIMBED	
	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT	BEFORE TREATMENT	DURING TREATMENT
30-40 years 1 patient	35	1	0	2	0	20
40-50 years 1 patient	Steady ache	0-1	Good increase in exercise tolerance, but blocks and stairs not measured			
50-60 years 8 patients	16	2	1 caused pain	5 caused pain	15 caused pain	25 did not cause pain
60-70 years 10 patients	28	4	2 caused pain	6 caused pain	11 caused pain	20 did not cause pain
70-80 years 6 patients	12	3	6 caused pain	12 did not cause pain	13 caused pain	27 did not cause pain
80 plus 2 patients	3	2	3 caused pain	6 caused pain		

Acheson and Moe[1] found, in intact dogs and cats, that the intravenous injection of tetraethylammonium chloride, 25 milligrams per kilogram of body weight, increased the amplitude of the T wave and usually produced an associated RS-T segment change in which this segment sloped from a high or low position at the end of the S wave to the beginning of the augmented T wave. The electrocardiograms returned to normal in two to six minutes. This dose was several times larger than that used for humans. Numerous attempts have been made by us and by others to demonstrate electrocardiographic changes during and following administration of tetraethylammonium chloride to man, but none have been seen.[8] Therefore, it would not seem that reversion of the electrocardiogram to its pre-anginal appearance can be attributed to any effect of the drug on the electrocardiogram other than that of terminating the anginal attack.

Simultaneous blood pressure, pulse, and venous pressure readings were recorded for twenty-three minutes after the administration of the usual dose of tetraethylammonium chloride to nine angina patients. The average changes are represented graphically in Fig. 5. Since we did not use as large doses of tetraethylammonium chloride as those used in treating peripheral vascular disease and in testing hypertensive patients,[5,12] these changes were in general not as great.

Since tetraethylammonium chloride gives a marked sensory stimulus, and since many anginal patients have a psychic make-up rendering them highly responsive to suggestion, it was thought that this factor should be evaluated.

Eleven of the twenty-five patients who had shown improvement on tetraethylammonium chloride were given placebos of intravenous calcium gluconate

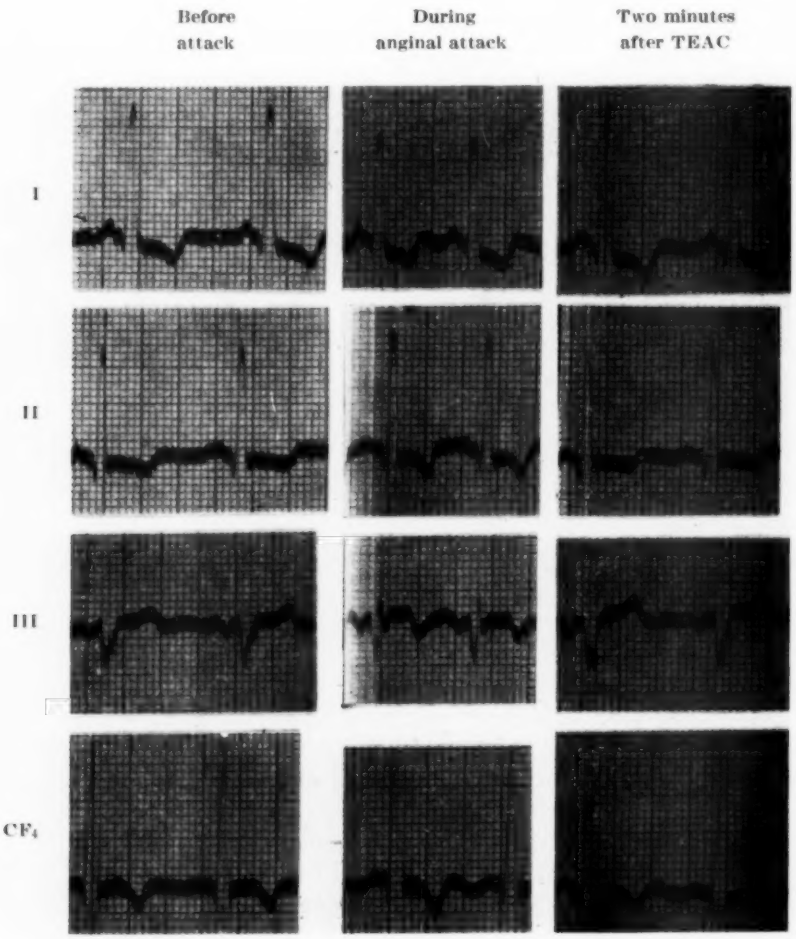

Fig. 1.—Electrocardiogram of a patient whose anginal attacks usually last about ten minutes if he does not take nitroglycerin. Note more depression of RS-T_2, more inversion of T_2, and inversion of T_3 during attack. These return to preanginal appearance two minutes after intravenous tetraethylammonium chloride.

or, if they were on digitalis, nicotinic acid in sufficient doses to give a good sensory stimulus. This was continued for five to eleven weeks. Neither of these are completely inert placebos. Calcium gluconate has been advocated by some in the treatment of angina,[13] and nicotinic acid has vasodilator effects which may be of benefit. However, they seemed to be the best substances available to us which would give a somewhat similar sensory stimulus, and they have no known harmful

effects in these patients. Four patients who had responded to tetraethylammonium chloride were no better on placebos then before either treatment. Six were better on tetraethylammonium chloride than on the placebo, but were better on the placebo than without either. One showed as much response to the placebo as to tetraethylammonium chloride.

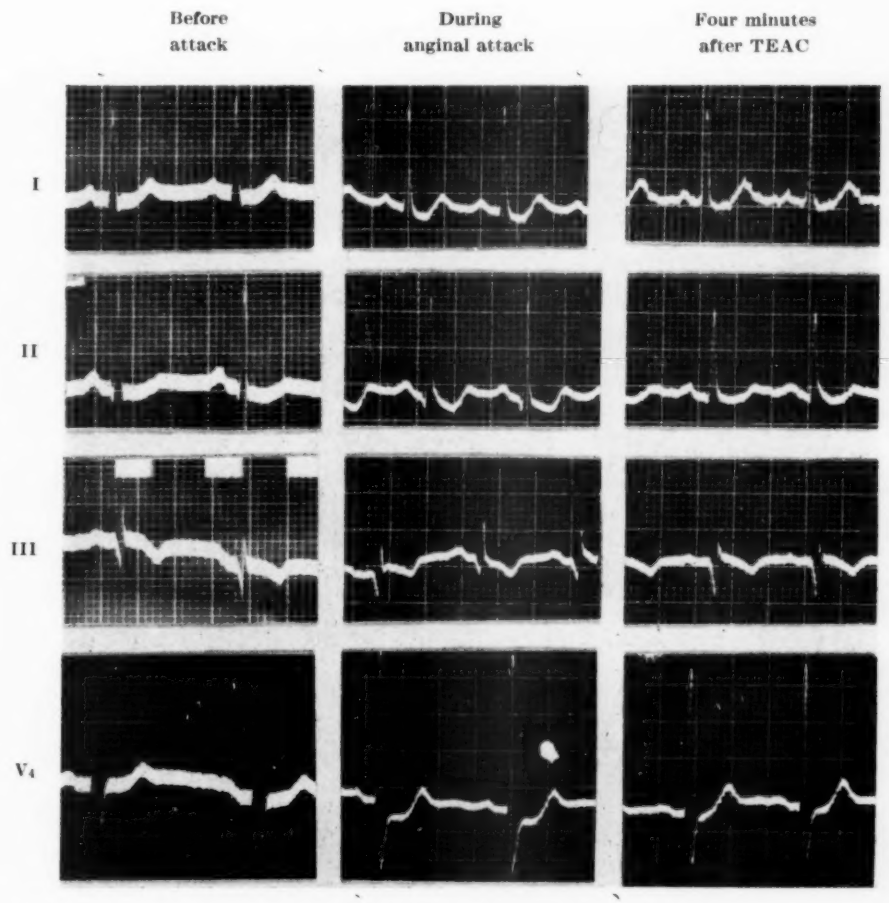

Fig. 2.—Electrocardiogram of a patient whose anginal attacks usually last about fifteen minutes if he does not use nitroglycerin. Note depression of RS-T segments in Leads I, II and V_4 during attack which disappears within four minutes after intravenous tetraethylammonium chloride.

This suggests that, although psychic stimulus does play a part in some patients (65 per cent of the small number tried), it probably was not the only factor responsible for improvement in the majority of those who responded to the drug (only 10 per cent did as well on placebos as on tetraethylammonium chloride).

Four of the patients in this series have died. In two, death occurred after the patients had been on placebos for five and seven weeks, respectively. In the

other two, death occurred two and five weeks after their last treatments with tetraethylammonium chloride and was not, as far as we could determine, due to any ill effects of the drug.

DISCUSSION

There are several possible explanations for termination of an attack of anginal pain by tetraethylammonium chloride and for the subsequent decreased number of attacks.

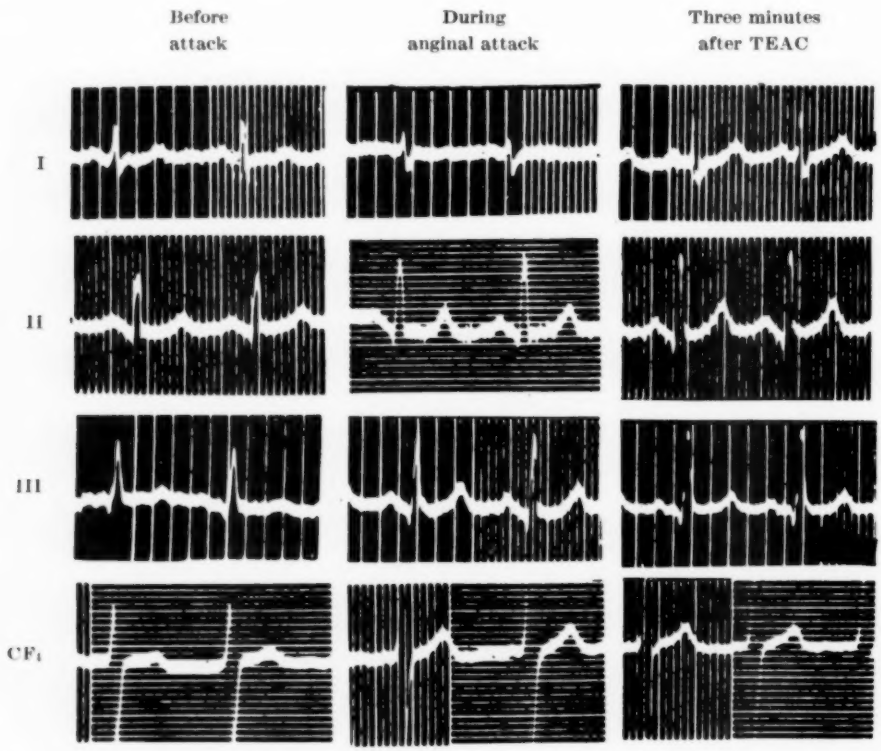

Fig. 3.—Electrocardiogram of a patient who has isolectic T_1 during anginal attack which becomes upright within three minutes after intravenous tetraethylammonium chloride.

1. *Actual increased blood supply to the myocardium.*—a.) Breaking up a reflex arc at autonomic ganglia so that the cycle of pain, vasoconstriction (or inhibition of compensatory dilatation of collateral circulation[14]), and more pain stimuli is interrupted. This explanation seems especially likely in view of the long-lasting symptomatic improvement despite the very transient action of the drug. b.) Increased cardiac output along with some decrease in venous pressure might augment coronary flow despite decreased blood pressure, especially if combined with the opening of more collateral circulatory channels. c.) Stimulation of vasodilator fibers.

2. *Decrease in work and oxygen consumption of myocardium.*—It should be noted that an increase in cardiac output after tetraethylammonium chloride does not necessarily mean that the heart is doing an increased amount of work, since it is actually working against less peripheral resistances and therefore able to pump the same amount of blood with less work.

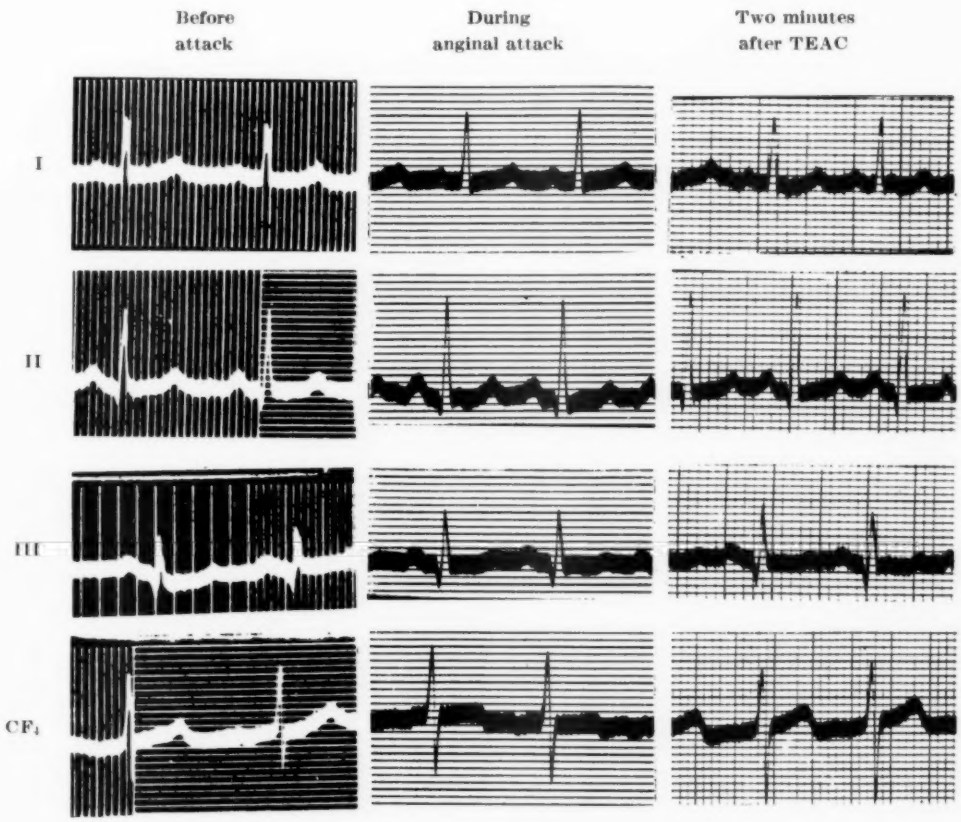

Fig. 4.—Electrocardiogram of a patient who had continuous anginal pain for three days and was not relieved by 30 nitroglycerin tablets. Note diphasic T in CF_4 during period of pain which became upright two minutes after intravenous tetraethylammonium chloride.

3. *Direct effect on the myocardium.*—It has been previously noted that the tetraethylammonium ion has some direct action on heart muscle resulting in improvement of its work capacity,[1,2] and that it acts peripheral to the nerves to antagonize the depressant action of drugs such as acetylcholine, pilocarpine, and potassium. In peripheral vascular disease, Coller and associates[16] have suggested modified tissue metabolism of an unknown nature as a possible explanation for the effect. There may be other direct effects on the heart muscle which have not been discovered.

4. *Blocking transmission of pain stimuli over afferent nerves to pain centers without increasing myocardial blood flow.*—a.) Could this occur at a synapse in the cord as there is no synapse in the ganglia? b.) Decrease in sensitivity of pain end organs in adventitia of coronary vessels (increased threshold).

5. *Decrease in circulating "pain substance" by some unknown mechanism.*

The fourth and fifth possibilities seem very unlikely, especially since many types of visceral pain are not relieved by tetraethylammonium chloride.

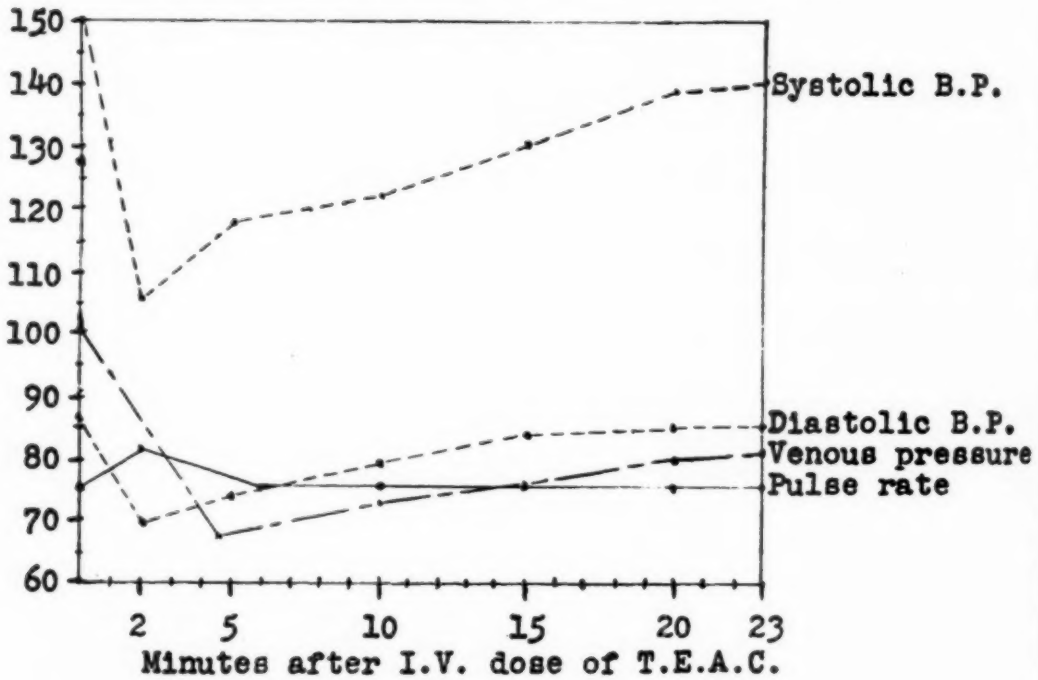

Fig. 5.—Average blood pressure, pulse, and venous pressure changes in nine patients receiving their usual dose of tetraethylammonium chloride for angina pectoris.

6. *Psychic stimulus.*—Since tetraethylammonium chloride is a potent sensory stimulant, and since many anginal patients have a psychic make-up susceptible to psychotherapy, this factor might help to explain the decrease in number and severity of attacks and increase in exercise tolerance. It probably would not account for the immediate termination of an attack of anginal pain as is seen with tetraethylammonium chloride.

SUMMARY AND CONCLUSIONS

1. Twenty-eight patients with angina pectoris have been treated with tetraethylammonium chloride and twenty-five of these patients have shown symptomatic improvement, as judged by a decrease in the number of anginal and allied attacks per week and by an increase in exercise tolerance. Of those

who improved, 65 per cent showed a significant decrease in the number of attacks and 60 per cent showed a noticeable increase in exercise tolerance.

2. Psychogenic effects of the marked sensory stimulus obtained with intravenous tetraethylammonium chloride seem to play a part in the beneficial effects. However, this was thought to be merely a contributory factor, since only one of eleven patients did as well on other drugs which give a sensory stimulus.

3. Sixty-five per cent of the twenty-eight patients on this treatment have been followed for periods varying from six to twenty months. No harmful effects attributable to the administration of the drug could be noted, despite the fact that 65 per cent of the patients were over 60 years of age and over 70 per cent had either experienced a myocardial infarct previous to this study or had been in congestive failure at some time (20 per cent had had both infarction and failure).

4. The importance of judging the correct dose for each patient individually is stressed. With this method the blood pressure and pulse changes were usually not very great, but patients must remain recumbent until they no longer have postural hypotension.

5. Especially gratifying was the relief of status anginosus and persistent, long-continued aching pain and discomfort associated with coronary insufficiency.

6. Electrocardiograms on four patients taken before anginal attacks, during an attack and two to four minutes after the intravenous administration of tetraethylammonium chloride are presented. These show an anginal pattern during the attack and reversion to the pre-anginal pattern immediately after administration of the drug. We believe that tetraethylammonium chloride actually breaks up the process involved in an anginal attack.

7. A discussion of possible mechanisms of action in terminating attacks and in giving prolonged improvement is presented.

8. In this small series, no conclusions can be drawn as to beneficial results other than symptomatic improvement. However, especially in patients for whom all other methods of treatment have proved to be inadequate, the additional relief obtained with tetraethylammonium chloride can be most gratifying.

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THE EFFECTS OF THE AGING PROCESS ON ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN THE MYOCARDIUM OF RATS

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THE knowledge that phosphocreatine assumes an important part in muscular contraction dates from the simultaneous and independent discovery of that compound by Fiske and Subbarow,[1] and by the Eggletons[2] in 1927. Since that time numerous investigations have served to place various components of the acid-soluble compounds of phosphorus in a role of prime importance in the mechanism of muscular contraction.

Phosphorus exists in muscle tissue in a variety of compounds. When muscle tissue is extracted with a 5 per cent solution of trichloracetic acid, a separation of two categories of compounds containing phosphorus is achieved. The phosphorus in the acid-insoluble fraction represents phospholipid, such as cephalin, lecithin, and sphingomyelin, the exact functions of which remain unsettled. The acid-soluble compounds, depending on their differential solubility as barium salts, are separable into two fractions. The barium-soluble portion contains the phosphorus present in phosphocreatine and hexosemonophosphates. The barium-insoluble portion contains inorganic phosphorus and phosphorus present in adenosine polyphosphates.

Although the importance of these compounds has been established, few investigations have dealt with the effects of the aging process on the distribution of phosphorus in muscle tissue. The published studies have been performed largely on skeletal muscle, and no data on cardiac muscle were found in a search of the literature. The present article deals with studies of the distribution of acid-soluble phosphorus compounds in heart muscle, as influenced by the aging process.

METHODS

Analyses were performed on the intact hearts of a total of thirty-two albino rats. The animals were a standardized group of rats (Sprague-Dawley), varying in age from 6 months to 30 months, and were kept under uniform environmental and dietary conditions. The animals were anesthetized with intraperitoneal injections of sodium pentobarbital. The heart was exposed, excised, blotted free from gross blood, and weighed rapidly on a microtorsion balance. It was then immersed immediately in a mixture of 5 c.c. of N/4 trichloracetic acid and washed sand contained in a mortar and chilled to a temperature of approximately

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TABLE I. DISTRIBUTION OF MYOCARDIAL ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN YOUNG AND MATURE RATS
(ALL VALUES ARE EXPRESSED AS MILLIGRAMS PHOSPHORUS PER 100 GRAMS WET TISSUE)

	YOUNG ANIMALS (60 DAYS-100 DAYS)						MATURE ANIMALS (6 MONTHS-9 MONTHS)								
ANIMAL NUMBER	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9
Total acid-soluble phosphorus	85.8	99.2	102.5	110.3	118.5	121.7	81.5	84.0	89.9	98.7	101.6	81.6	79.3	83.7	80.7
Creatine phosphate	8.4	8.1	8.5	6.9	6.6	9.1	9.5	10.0	9.1	10.4	8.0	6.3	6.9	11.9	6.1
Hexose phosphate	37.5	34.0	34.8	34.6	37.3	39.3	18.4	20.9	25.6	30.2	30.7	18.8	19.6	9.4	15.5
Ortho phosphate	28.5	29.9	33.9	37.5	28.6	28.5	34.9	39.5	30.9	31.2	33.4	36.0	29.8	32.4	36.0
Adenosine triphosphate	20.5	19.1	23.7	16.7	19.4	17.2	16.7	10.9	18.1	25.8	17.2	20.2	20.0	21.4	18.9
Total phosphate insoluble fraction	35.6	54.8	57.6	66.4	71.5	73.2	52.8	54.1	56.8	58.7	62.9	57.9	50.7	59.4	61.3
Heart weight (mg.)	401	421	461	413	538	320	676	693	796	652	790	793	756	681	919
Body weight (Gm.)	105	115	140	125	168	76	235	240	230	225	275	274	295	275	330

TABLE II. DISTRIBUTION OF MYOCARDIAL ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN OLD AND SENILE RATS
(ALL VALUES ARE EXPRESSED AS MILLIGRAMS PHOSPHORUS PER 100 GRAMS WET TISSUE)

	OLD ANIMALS (18 MONTHS-24 MONTHS)									SENILE ANIMALS (24 MONTHS-30 MONTHS)							
ANIMAL NUMBER	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8
Total acid-soluble phosphorus	78.8	91.9	86.7	79.9	85.1	81.0	92.8	75.3	80.7	74.6	76.5	79.8	87.8	72.7	77.0	79.1	79.8
Creatine phosphate	5.9	4.2	5.8	6.0	4.5	5.0	4.2	4.2	4.3	4.1	3.5	4.9	6.5	5.0	4.6	5.2	4.1
Hexose phosphate	19.8	30.2	19.4	16.4	18.0	26.0	29.0	15.7	18.7	13.6	15.6	16.1	24.3	18.2	16.6	20.1	18.4
Ortho phosphate	34.1	43.0	43.8	31.4	39.8	31.6	38.1	32.0	37.8	34.5	37.2	34.7	35.0	29.9	32.3	34.4	36.0
Adenosine triphosphate	13.3	9.7	20.8	26.5	18.8	15.9	15.5	23.3	18.0	19.4	18.5	17.4	21.7	21.1	22.1	17.3	16.6
Total phosphorus insoluble fraction	53.5	57.7	68.7	54.6	62.4	56.2	59.6	56.2	57.7	58.3	59.6	52.3	59.0	54.1	57.5	51.9	55.4
Heart weight (mg.)	1470	940	1124	1123	1021	1044	904	1463	1189	1262	1093	833	954	1081	1037	1098	1024
Body weight (Gm.)	425	380	403	405	365	365	360	520	440	465	390	387	380	467	450	418	380

0.5° centigrade. The time interval elapsing from the initial thoracic incision to the immersion of the heart into the acid solution averaged approximately 45 seconds. The heart was macerated quickly and the analyses for the various phosphate fractions were performed essentially according to the procedure described by Eggleton and Eggleton.[3] Phosphate was determined by the colorimetric method of Fiske and Subbarow,[4] employing the Evelyn photoelectric colorimeter.

RESULTS

The thirty-two animals upon which analyses were performed are divided into four age groups. The results are seen in Tables I and II. The approximate ages of the animals in the four groups are: (Table I) young animals, 60 days to 100 days; mature animals, 6 months to 9 months; (Table II) old animals, 18 months to 24 months; senile animals, 24 months to 30 months.

Statistical evaluations[5] of all data are shown in Tables III and IV. The analyses on the senile and young animals were performed simultaneously, and thus these two age groups are examined together. At another time simultaneous analyses were performed on the mature and young animals, and thus they are examined together.

Total Acid-Soluble Phosphorus.—The findings in cardiac muscle, in the present study, are quite different from those reported by others in skeletal muscle (see p. 358). The data in Tables III and IV appear to indicate that the youngest animals possess the greatest concentration of acid-soluble phosphorus (mean value of 106.3 mg. per cent). The mean value of the mature age group is 86.7 mg. per cent; that of the old age group is 83.5 mg. per cent; and of the senile group, 78.6 mg. per cent. Nevertheless, these differences do not appear to be statistically significant.

Barium-Soluble Phosphates.—

Creatine Phosphate: The results on the phosphocreatine content of rat myocardium, as seen in Tables III and IV, are at marked variance with the data on rat skeletal muscle. The concentration of the phosphorus in the phosphocreatine of the hearts of the young and mature animals is significantly greater (mean values of 8.6 mg. per cent and 7.9 mg. per cent) than that of the old and senile animals (mean values of 4.9 mg. per cent and 4.7 mg. per cent). Thus the aging process in the rat myocardium appears to be attended by a marked and significant decline in the phosphocreatine phosphate fraction (Fig. 1).

Hexosephosphates—Barium-Soluble Fraction: This fraction contains the phosphorus present in hexosemonophosphate and other unknown barium-soluble esters. Statistical analysis (Tables III and IV) reveals the hexosephosphate concentration in young animals (mean value of 36.2 mg. per cent) to be significantly and markedly greater than that of the older age groups. The mean value of the mature animals is 21.4 mg. per cent, of the old animals 20.0 mg. per cent, and of the senile animals 18.1 mg. per cent. Thus after an initial significant decine after the first 100 days of life, the hexosephosphate concentrations exhibit minor fluctuations with advancing age (Fig. 2).

TABLE III. STATISTICAL COMPARISON OF DISTRIBUTION OF MYOCARDIAL ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN SENILE AND YOUNG RATS

	SENILE ANIMALS (29 MONTHS-30 MONTHS)		YOUNG ANIMALS (60 DAYS-100 DAYS)		DIFFERENCE IN THE RESPECTIVE MEAN VALUES OF THE TWO GROUPS	STANDARD ERROR OF THE DIFFERENCE OF MEAN VALUES	VALUES OF "T"†	REMARKS
	MEAN	S.D.*	MEAN	S.D.*				
Total acid-soluble phosphate	78.6	±11.16	106.3	±22.11	+27.7	±22.9	1.20	Not significant
Creatine phosphate	4.7	±0.24	7.9	±1.64	+3.2	±1.63	2.0	Significant
Hexose phosphate	18.1	±3.83	36.2	±7.35	+18.1	±7.61	2.36	Significant
Ortho phosphate	34.3	±2.22	31.1	±6.61	−3.2	±5.6	0.57	Not significant
Adenosine triphosphate	19.2	±2.92	19.4	±6.09	+0.2	±4.2	0.04	Not significant
Total phosphate insoluble fraction	56.0	±6.86	59.8	±22.11	+3.8	±13.6	0.02	Not significant

*Standard deviation.
†"T" is calculated by dividing the difference in the mean values by their standard errors.

TABLE IV. STATISTICAL COMPARISON OF DISTRIBUTION OF MYOCARDIAL ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN MATURE AND OLD ANIMALS

	MATURE ANIMALS (6 MONTHS-9 MONTHS)		OLD ANIMALS (18 MONTHS-24 MONTHS)		DIFFERENCE IN THE RESPECTIVE MEAN VALUES OF THE TWO GROUPS	STANDARD ERROR OF THE DIFFERENCE OF MEAN VALUES	VALUES OF "T"†	REMARKS
	MEAN	S.D.*	MEAN	S.D.*				
Total acid soluble phosphorus	86.7	±11.42	83.5	±10.24	−3.2	±14.46	0.22	Not significant
Creatine phosphate	8.6	±1.31	4.9	±0.21	−3.7	±1.39	2.66	Significant
Hexose phosphate	21.4	±3.25	20.9	±3.60	−1.2	±4.53	0.26	Not significant
Ortho phosphate	33.7	±4.46	36.8	±4.95	−3.1	±6.28	0.50	Not significant
Adenosine triphosphate	18.8	±2.69	17.3	±6.60	−1.5	±3.54	0.42	Not significant
Total phosphate insoluble fraction	57.1	±7.80	56.5	±9.30	−0.6	±11.45	0.05	Not significant

*Standard deviation.
†"T" is calculated by dividing the difference in the mean values by their standard errors.

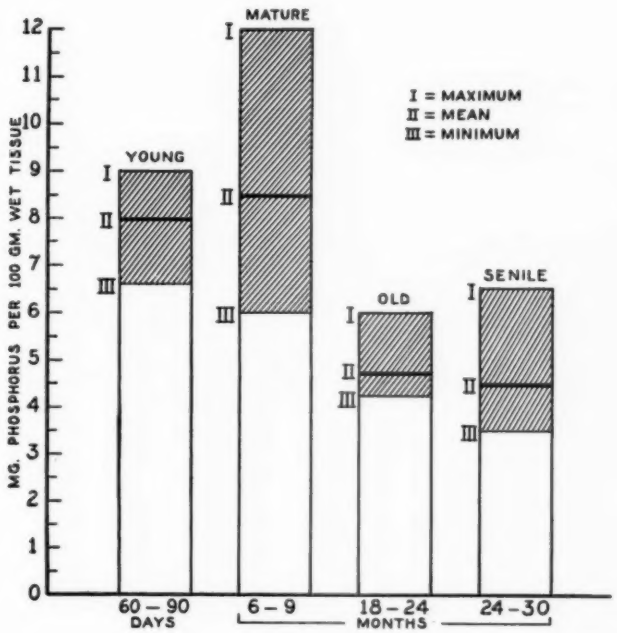

Fig. 1.—The myocardial creatine phosphate content in various life stages is shown.

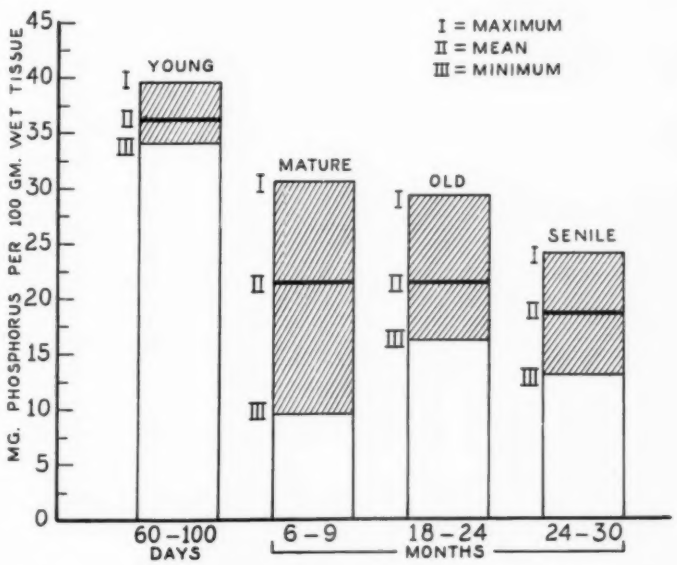

Fig. 2.—The myocardial hexosephosphate content in various life stages is shown.

Barium-Insoluble Phosphates.—

Orthophosphate: From Tables III and IV one sees the concentration of phosphorus in orthophosphate of all four groups to be relatively constant at approximately 34 mg. per cent.

Adenosine Triphosphate: No significant changes with age were noted in this fraction. The mean of all analyses being 18.5 mg. per cent.

Total Phosphorus—Barium-Insoluble Portion: The concentrations in all four groups, as seen in Tables III and IV, are relatively constant at approximately 57.5 mg. per cent.

DISCUSSION

The alterations which have been mentioned were not related to dilution because in parallel experiments significant changes with age in the water content of the heart could not be demonstrated.

Total Acid-Soluble Phosphorus.—Pincussen, Reed, and Visscher[6] found the total acid-soluble phosphorus compounds of human skeletal muscle to increase progressively to 30 years of age, and to decrease after 40 years. Struck, Reed, and Cohen[7] reported a marked increase in the acid-soluble phosphorus content of rat skeletal muscle from 13 weeks to 43 weeks, with a definite decline from 43 weeks to 65 weeks. However, examination of their data on two groups of rats of the same age under similar dietary regimes, but used for experimental purposes at different times, reveals a value of 125 mg. of total acid-soluble phosphorus in one group, as compared to a value of 151 mg. for rats of similar age in another group. Thus the question of additional variables has been raised.[8] A relatively constant concentration in the total acid-soluble phosphorus content of adult muscle tissue, even during muscular contraction, was found by Cuthbertson.[9] In the most complete and rigidly controlled studies to date, Horvath[8] reported a 100 per cent increase in the first 5 weeks of life in rat skeletal muscle, followed by a slow rise to the adult average at approximately 100 days. In old age, minor fluctuations occurred.

The findings in the present study indicate a relatively constant concentration of acid-soluble phosphorus in rat myocardium throughout life. This is in agreement with some of the cited studies on skeletal muscle.

Barium-Soluble Phosphates.—

Creatine Phosphate: Several investigations on the quantitative change in the phosphocreatine content of muscles in the embryonic, young, and old stages of life have been reported. The work of Cole and Koch,[10] in their studies on the effects of age, diet, and irradiated ergosterol on the phosphorus distribution in the gastrocnemius muscle of rats ranging in age from 21 to 168 days, showed that the phosphocreatine content rapidly increased from birth to three weeks after weaning, and then remained relatively constant for the remaining study period of 168 days. Studies on the chick embryo (Baldwin and Needham[11]) showed phosphocreatine to be present in small amounts, with subsequent rapid increases following hatching. The excellent studies of Horvath[8] on a total of 409 albino rats, ranging in age from 3 days to 768 days, reveal the phosphorus in the

phosphocreatine to increase from 22 mg. per cent to 57 mg. per cent within the first 40 days of the rat's life. During adult life and into old age, the concentration remains relatively constant at approximately 60 mg. per cent of phosphorus.

This study was undertaken as part of an experimental approach to the question of why the human organism with advancing age undergoes an increasing predisposition to a diminution in the reserve capacity of the heart. Although the assumption that 10 days of a rat's life are equivalent to one year in the life of a man is a gross approximation, it may be used to compare the latter stages of life in both species. Thus the human equivalents in the four groups of rats presented in Tables I and II are: young animals, 6 years to 10 years; mature animals, 18 years to 27 years; old animals, 54 years to 72 years; senile animals, 72 years to 90 years.

The aging process in the heart of the rat is not attended by limitations in the availability of the adenosine polyphosphates. In recent years the position of phosphocreatine in the scheme has been established as being a reserve or storehouse for the energy-rich phosphate bonds normally furnished by the adenosine polyphosphates (ATP and ADP). Thus if the energy demands of the muscle are such that for the moment the normal means of reconstituting ATP are inadequate, then phosphocreatine is called upon to donate its energy-rich phosphate bond for this purpose.

Our results as seen in Tables I to IV and in Fig. 1 show a significant diminution in the concentration of phosphorus as phosphocreatine in the myocardium with the attainment of old age in the rat. Thus the aging process produces a situation in which the chemical reserve is markedly depleted and by so doing may functionally reduce the reserve capacity of the heart.

Bodansky and Duff,[13] in their study of age as a factor in the resistance of the albino rat to thyroxine, found that young rats apparently stand losses of the creatine content of the myocardium better than do old animals. Although the employment of the creatine content of tissue as an index of the phosphocreatine content is open to some question, their observations could be interpreted as indicating that the better resistance of the young heart to thyrotoxicosis is related to the higher content in phosphocreatine.

Horvath,[8] in his study of the effects of aging on the acid-soluble phosphorus compounds in rat skeletal muscle, found no diminution in phosphocreatine, and on the basis of his results concluded that there were excellent biochemical conditions still present in the aged muscle for the performance of work. These results when compared to our data on cardiac tissue are not too surprising when one considers that cardiac and skeletal muscles differ strikingly in many other physiological and chemical aspects.

Hexosephosphates—Barium-Soluble Fraction: Horvath[8] reported a slight increase in hexosephosphate concentration from youth to adult life in rat gastrocnemius muscle, but the changes are not striking when expressed in per cent of total acid-soluble phosphorus. The significance of our finding that the onset of maturity is accompanied by a well-marked decline in hexosephosphate is uncertain.

Barium-Insoluble Phosphates.—Analysis of this portion has given variable results. In 27 of 32 analyses given in Tables I and II, the sum of the inorganic phosphorus, plus three-halves of the easily hydrolized phosphorus (assuming all the latter present as adenosine triphosphate) is greater than the total phosphorus. In twenty of these the discrepancy is greater than may be accounted for by the inherent error in calculation of the fractions by difference. It seems likely that the error is not in the determination of total phosphorus of this portion, as this total, plus that of the barium-soluble phosphates, closely approximates the total phosphate of the original trichloracetic acid filtrates. Similar difficulties with this fraction have been noted in dog skeletal and cardiac muscle by Pollack and his co-workers,[12] and in rat skeletal muscle by Horvath.[8] In any event, no significant changes with age were observed.

SUMMARY

1. Analyses of the various components of the acid-soluble phosphorus compounds of the myocardium were performed in the young, mature, old, and senile stages of life in the albino rat.

2. A marked and significant reduction of the barium-soluble hexose-phosphate content of rat myocardium occurs with the onset of maturity. With advancing age the concentrations remain relatively constant.

3. The phosphocreatine concentrations exhibit a marked and significant decline with the attainment of old age in the rat.

4. Significant alterations in other acid-soluble phosphorus fractions were not encountered.

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TRANSIENT VENTRICULAR FIBRILLATION

III. The Effects of Bodily Rest, Atropine Sulfate, and Exercise on Patients With Transient Ventricular Fibrillation During Established Auriculoventricular Dissociation. A Study of the Influence of the Extrinsic Nerves on the Idioventricular Pacemaker of the Heart

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IT IS apparent from prolonged observations on the preliminary events that lead to the onset of transient ventricular fibrillation in patients with established A-V dissociation, that some of the alterations in the cardiac mechanism must be due to changes in the rate and rhythm of the idioventricular pacemaker of the heart. On numerous occasions such changes, consisting of an acceleration of the idioventricular rate, appeared shortly before the onset of transient seizures of ventricular fibrillation.[1] More recently, such seizures were noted to appear spontaneously after *slowing* or after alternate slowing and acceleration of the ventricular rate. Frequently, after some forms of undue exertion, some of these patients were observed to have slower ventricular rates during A-V dissociation and shortly thereafter developed transient periods of ventricular fibrillation.

It was the purpose of this study to inquire into the part played by the extrinsic nerves of the heart in the development of these variations in the idioventricular pacemaker and to determine to what extent these periods of transient ventricular fibrillation were due either directly or indirectly to their influence.

REVIEW OF LITERATURE

In experimentally produced A-V dissociation, stimulation of the vagus nerves may yield an inhibitory action of the centers that regulate the idioventricular pacemaker of the heart and thus slow the ventricles.[2] Such slowing may occur through the vagus itself[3] or through factors which may influence the vagus reflexly through the carotid sinus, such as changes in respirations or sudden variations in blood pressure.[4] However, since atropine was found to have no effects on the ventricles in the presence of experimental heart block, some observers concluded that the ventricles were not innervated by vagal fibers.[5]

Clinicians have likewise differed in their opinions on the influence of the extrinsic cardiac nerves on the ventricular rate during A-V dissociation. Lewis,

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for example, states that "in most clinical cases of complete heart block, the idioventricular rhythm is uncontrolled by the vagus, but that in some patients, especially young patients, it is controlled in some degree."[6] Only recently Taussig[7] emphasized the fact that, although in adults exercise has no effect upon the idioventricular rate, in children exercise usually causes an acceleration of ten to twenty beats per minute. She remarks that the effects of atropine are closely similar to those of exercise and that in adults with complete heart block "atropine even in large doses seldom alters the idioventricular rate and rhythm." Again, others have accepted the failure to note acceleration of the ventricles after atropine as further proof of the absence of vagal control of the ventricles in established heart block.[8]

More recently Boas and Goldschmidt[9] and subsequently Boas[10] presented evidence that the spontaneous variations in complete heart block in response to sleep, exercise, and other influences "are analogous to and expressed in percentage changes in rate, are of the same magnitude as the changes in the sinus rhythm under similar circumstances." Their observations were enhanced by Gilchrist[11] who noted that in patients with established A-V dissociation the idioventricular rate varied from day to day and that each individual has his own peculiar range of rate and rhythm in response to bodily rest, exercise, fever induced by the intravenous use of typhoid vaccine, or by atropine sulfate in adequate doses. Other reported clinical instances of heart block with variations in the ventricular rate associated with changes in posture[12] or acceleration of the ventricles after exercise[13-15] indicate graphically that there are definite changes in both rate and rhythm inherent in the idioventricular pacemaker of the heart during established A-V dissociation.

Note is made that, with rare exceptions, electrocardiograms obtained in the cases cited above showed that the changes in the ventricular rate were not to be attributed to a shift in the idioventricular pacemaker from the A-V node to the lower centers in the ventricles, since the ventricular complexes recorded before or after such changes were all alike in shape, size, and form, from beat to beat.

METHOD OF STUDY

The natural course of the rate and rhythm of three patients[16] who were subject to transient seizures of ventricular fibrillation during established A-V dissociation was studied over a prolonged period of time. Correlated observations were made between the alterations in the heart rate and rhythm at different intervals during the patients' stay in the hospital while they were attached to the electrocardiographic circuit, and numerous records were obtained for study. On some occasions, heart counts and records were taken at frequent intervals for as long as eight consecutive hours.

Particular attention was paid to the influence of emotional factors, such as excitement or the introduction of a needle in a vein, or the variations in the idioventricular pacemaker of the heart during bodily rest and while the patients were sound asleep.

The effects of both moderate exercises and undue forms of exertion on the idioventricular rate and rhythm were correlated with the changes observed in the

electrocardiogram. In two patients who were bedridden the exercise consisted of bending the body trunk forward and backward to the point of fatigue. In one patient, who was able to be up and about and who had experienced several seizures of transient ventricular fibrillation following the type of exertion associated with "straining at stool" or when walking rapidly up an incline, several forms of exertion were studied. At first his heart rate and rhythm were investigated while be was in bed with his right leg attached to weights by a pulley system. By bending his leg at the knee and lifting the weights it was possible to note the effects of such forms of muscular strain upon the heart. Forms of undue exertion were brought about by having the patient step up and down on a bench 12 inches from the floor until he was fatigued or complained of pains and dyspnea. Continuous records were obtained prior, during, and subsequent to these forms of exertion for as long as one-half hour after the onset of the experiment. After that, records were obtained at frequent intervals for as long as four hours.

Carotid sinus pressure, eyeball pressure, and blood pressure changes were noted during and subsequent to these various experiments.

Finally, atropine sulfate (grain 1/30) was injected intravenously during bed rest and prior to, as well as subsequent to, these various forms of exertion. In one patient this drug was used to test the effects of induced (with epinephrine hydrochloride) forms of acceleration of the idioventricular pacemaker on extrasystoles of the heart.[17]

CHANGES IN THE IDIOVENTRICULAR RATE AND RHYTHM DURING BODILY REST

Two distinct types of mechanisms were observed in the idioventricular rate and rhythm of the three patients during bodily rest. In one the ventricular rate was "relatively fixed" and the rhythm was regular. The rate did not fluctuate more than an average of 5 to 8 beats per minute for long periods when the rate was counted either during the day or at night during sleep. In this respect the behavior of the A-V pacemaker of the heart was similar to that described by Gilchrist[11] and by Boas[10] in the usual patient with established A-V dissociation; this was considered by them to be a normal variation which was to be expected in such patients. At this rate of beating the patients were comfortable and their electrocardiograms revealed the ventricular complexes to be of the supraventricular form.

The second type of variation consisted of an unusually "labile fluctuation" in the rate of the ventricles that was associated with signs and symptoms of uneasiness in the chest, sighing respirations, shortness of breath on mild exertion, and frequently short periods of giddiness and "blackouts" with recurring "coupling" of heart beats. This condition would last for days at a time and was sufficiently incapacitating to prevent these patients from being up and about. This cardiac mechanism ended with transient periods of ventricular fibrillation or reverted to the "relatively fixed" variation and rhythm.

A detailed study of this form of "labile" mechanism revealed several types of alterations in the idioventricular pacemaker that merit attention.

1. The most common change consisted of a progressive, uniform increase and decrease of the sphygmic interval from beat to beat in which all of the ventricular complexes were uniform in shape, size, and form and were of the supraventricular type. This mode of acceleration would come on suddenly and resulted as a rule from emotional disturbances such as the appearance of the physician,

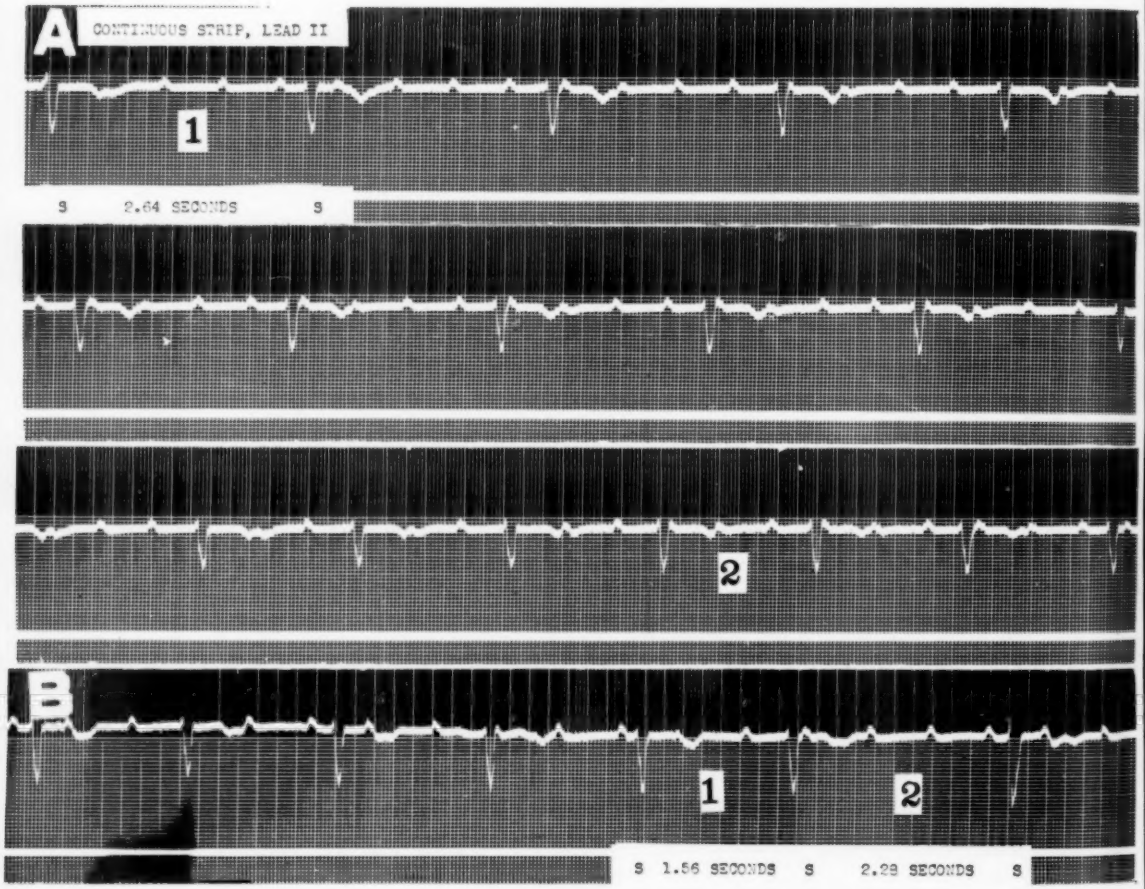

Fig. 1.—*A*, Continuous strip, Lead II. Progressive increase in the idioventricular rate as a result of an emotional disturbance from an average of 22.7 beats per minute (1) to 38.4 beats (2) in less than four seconds. The auricular rate is 100 beats per minute. *B*, Record showing the sudden reduction in the sphygmic interval from 1.56 seconds (1) to 2.28 seconds (2) after the patient became calm.

the introduction of a needle into a vein, or during an argument or conversational effort. For example, on one occasion, after prolonged bed rest, the ventricular rate of one patient averaged 22.7 beats per minute and the sphygmic interval measured 2.64 seconds (Fig. 1,*A*[1]). In less than four seconds after this patient was informed that he would receive an intravenous injection of atropine the ventricular rate increased progressively to 38.4 beats per minute, the sphygmic interval measuring now only 1.56 seconds with the more rapid rate. In the mean-

time the auricular rate which averaged 100 beats per minute remained the same throughout this period (Fig. 1,*A*[2]).

The decrease in the ventricular rate after such a progressive increase due to emotional factors was also gradual, and in only a matter of seconds the rate leveled off and the rhythm become regular. However, there were some slight variations from these gradual changes.

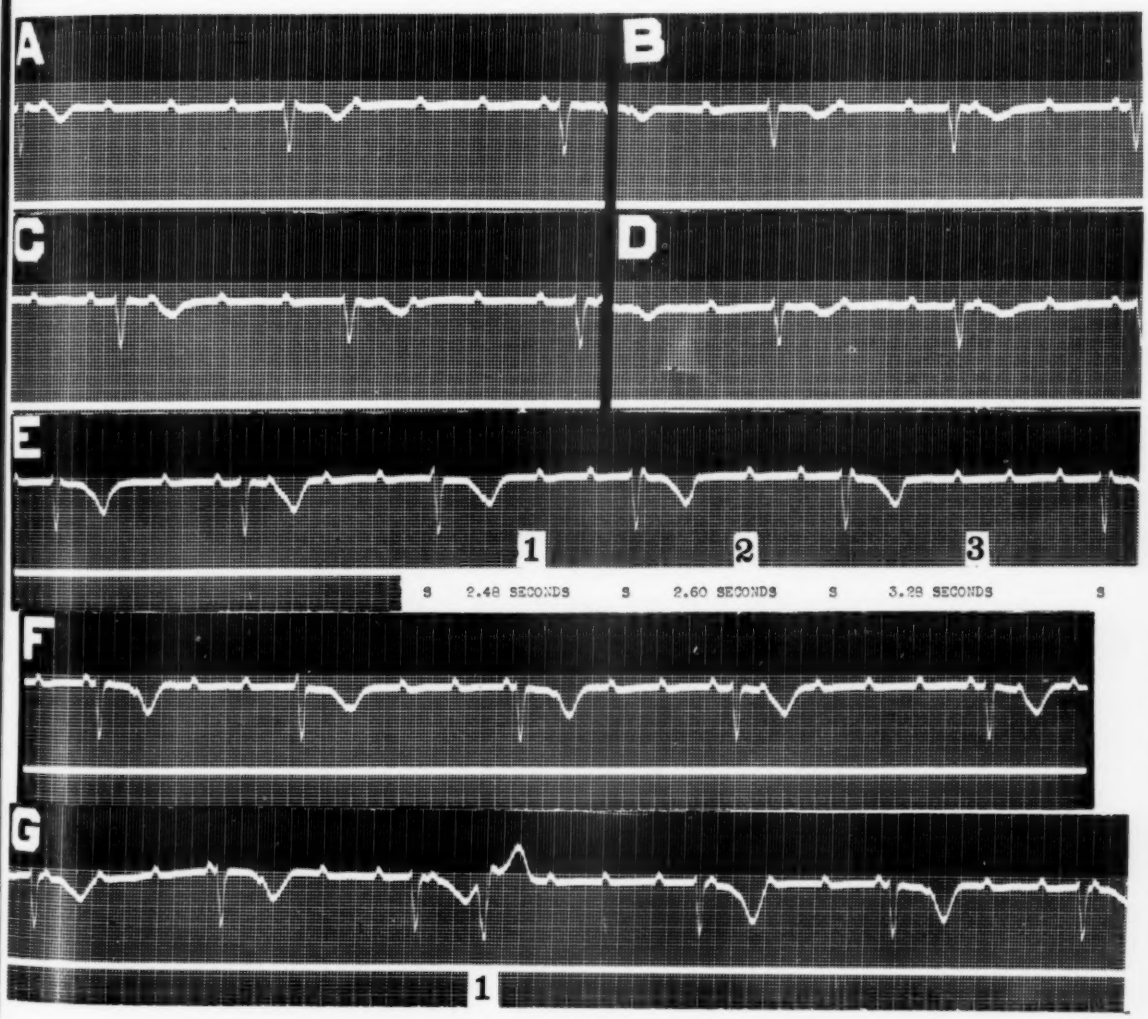

Fig. 2.—Record showing abrupt changes in the idioventricular rate and rhythm within a very short period. *A*, The auricular rate is 100 beats and the ventricular rate averages twenty beats. *B*, One second later, the auricles average 75 beats and the ventricles 30 beats per minute. *C*, Three minutes later, the auricles are 113 beats while the ventricles average 27.2 beats. *D*, Four seconds later the auricles are 75 beats and the ventricles 30 beats per minute. *E* and *F*, Progressive slowing of the sphygmic intervals alternating with abrupt changes sixty-eight seconds apart. *G*, Premature beats of the ventricles begin to appear after such changes in the idioventricular rate and rhythm.

2. Frequently the slowing of the ventricular rate following a progressive increase was abrupt. For example, in Fig. 1,*B*(1) the ventricular rate averages 38.4 beats per minute and the sphygmic interval measures 1.56 seconds. After five beats in the record at this rate there is an abrupt slowing of the ventricles to 26.3 beats per minute with the sphygmic interval measuring 2.28 seconds (Fig. 1,*B*[2]). This sudden change appeared without any provocation, the respirations and blood pressure remaining the same. This lower rate would last for a few minutes and then be replaced by the more rapid rate just as abruptly as it appeared.

Such abrupt changes in the auricular as well as ventricular rates were quite marked at times. In Fig. 2,*A* the auricular rate averages 100 beats per minute and the ventricular rate averages 20 beats while the rhythm is perfectly regular. Within one second the auricular rate fell to 75 beats per minute, while the ventricles averaged 30 beats (Fig. 2,*B*). Three minutes later the auricles beat at 113 beats per minute while the ventricles averaged 27.2 beats (Fig. 2,*C*). Again, within a matter of seconds, the auricles were lowered to 75 beats while the ventricles remained at 30 beats (Fig. 2,*D*).

Within the same half hour the auricles would beat at one time at the rate of 87.9 beats and the ventricles at 25 beats with a regular rhythm (Fig. 2,*E*). The sphygmic interval would gradually increase from beat to beat to 2.48 seconds (Fig. 2,*E*[1]), 2.60 seconds (Fig. 2,*E*[2]), and then to 3.28 seconds (Fig. 2,*E*[3]), and thus slow the ventricular rate to 18.2 beats per minute. Similar changes may be noted only a few seconds later in which the idioventricular beats vary from beat to beat so that there is a constant alternating, slowing, and acceleration of the ventricles (Fig. 2,*F*).

An even more pronounced change may be noted in Fig. 10,*A*(1), in which there is shown a prolonged pause, measuring 4.2 seconds at which the ventricular rate would average 14.2 beats per minute. This is terminated by a ventricular rate averaging 30.7 beats per minute. Again, note is made that the ventricular complexes are all of the supraventricular type and of the same size, shape, and form from beat to beat indicating that they arise from the same focus in the A-V node.

After the persistence of such alternation in rate and rhythm for awhile, although the main ventricular deflections in the electrocardiogram would remain of the same shape and size, there would develop progressive changes in the RS-T segments and the T waves, which became markedly inverted. (Compare the depth of the T waves in Fig. 2,*A* and *B* with that of the T waves in Fig. 2,*E*, *F*, and *G*).

Frequently, at such intervals, premature beats of the ventricles would begin to disrupt the rhythm. These would always appear at fixed distances from the idioventricular beats and invariably at the beginning of the T waves (Fig. 2,*G*[1]).

3. At times, especially during complete rest, there would appear a gradual increase and decrease in the sphygmic interval with an alteration in the rhythm in which the ventricular complexes in the electrocardiogram would be slightly different in size, shape, and form as well as in duration from beat to beat. In Fig. 3,*A*(1), the first sphygmic interval measures 2.36 seconds with the ven-

tricles averaging 25.4 beats per minute. The succeeding sphygmic intervals from the fourth beat on (Fig. 3,*A*[2]) are all different in range from beat to beat, the shortest interval measuring 1.84 seconds (Fig. 3,*A*[3]). The first three ventricular complexes are downwardly directed. They resemble each other except for the size of the T waves which decrease progressively in height. Beginning with the fourth ventricular complex, all are slightly different in size, shape, and form. It is very likely that these all arise from either one or the other of the bundles, indicating that these points of origin also have a range of fluctuation in rate and rhythm almost similar to that of the A-V node itself.

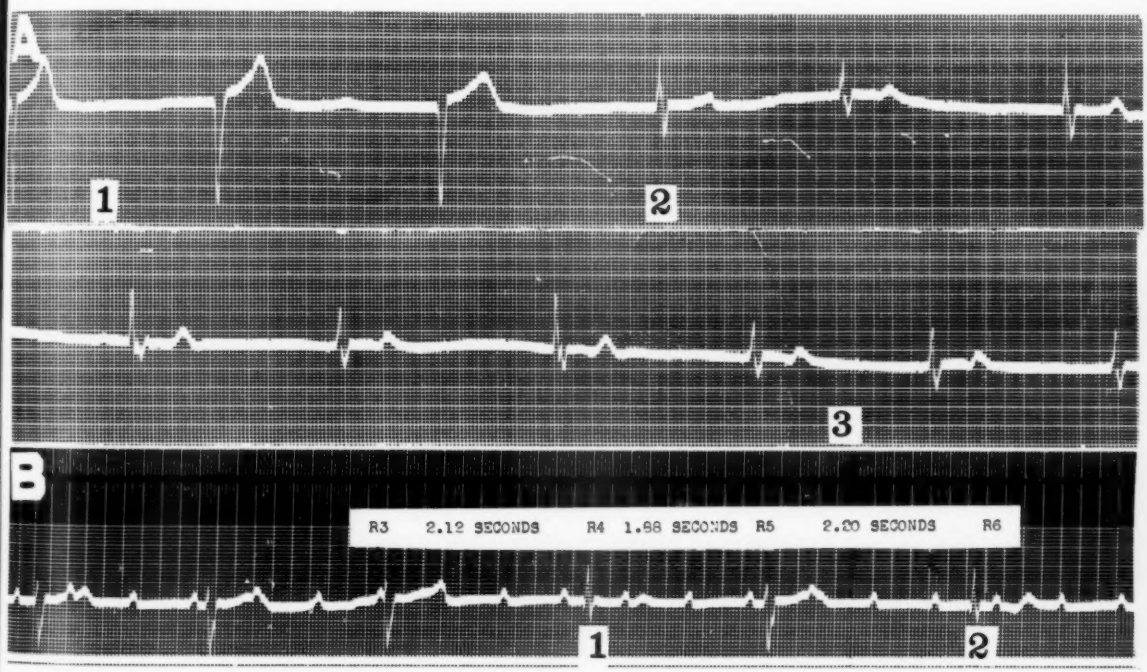

Fig. 3.—*A*, Continuous strip, Lead II. Note the changes in shape, size, and form of the ventricular deflections as well as variations in the idioventricular rhythm from beat to beat. *B*, Changes in the direction of the ventricular complexes associated with changes in the rate and rhythm of the idioventricular pacemaker of the heart. Note the variable sphygmic intervals.

4. More often there may be a sudden but periodic change in the idioventricular rate and rhythm in which a single beat with a ventricular complex that varies from the preceding and succeeding one suddenly disrupts the usual rhythm. In Fig. 3,*B*(1), R-4 (the R wave in the fourth ventricular beat on the strip) is different in shape, size, form, and direction from R-3, its preceding beat, and R-5, its succeeding beat. The interval between R-3 and R-4 measures 2.12 seconds whereas the interval between R-4 and R-5 measures 1.88 seconds. Again the interval between R-5 and R-6 measures 2.20 seconds. R-6 (Fig. 3,*B*[2]) resembles R-4 but is different from R-5, its preceding beat. Although R-4 and R-6 of this record have ventricular complexes supraventricular in form.

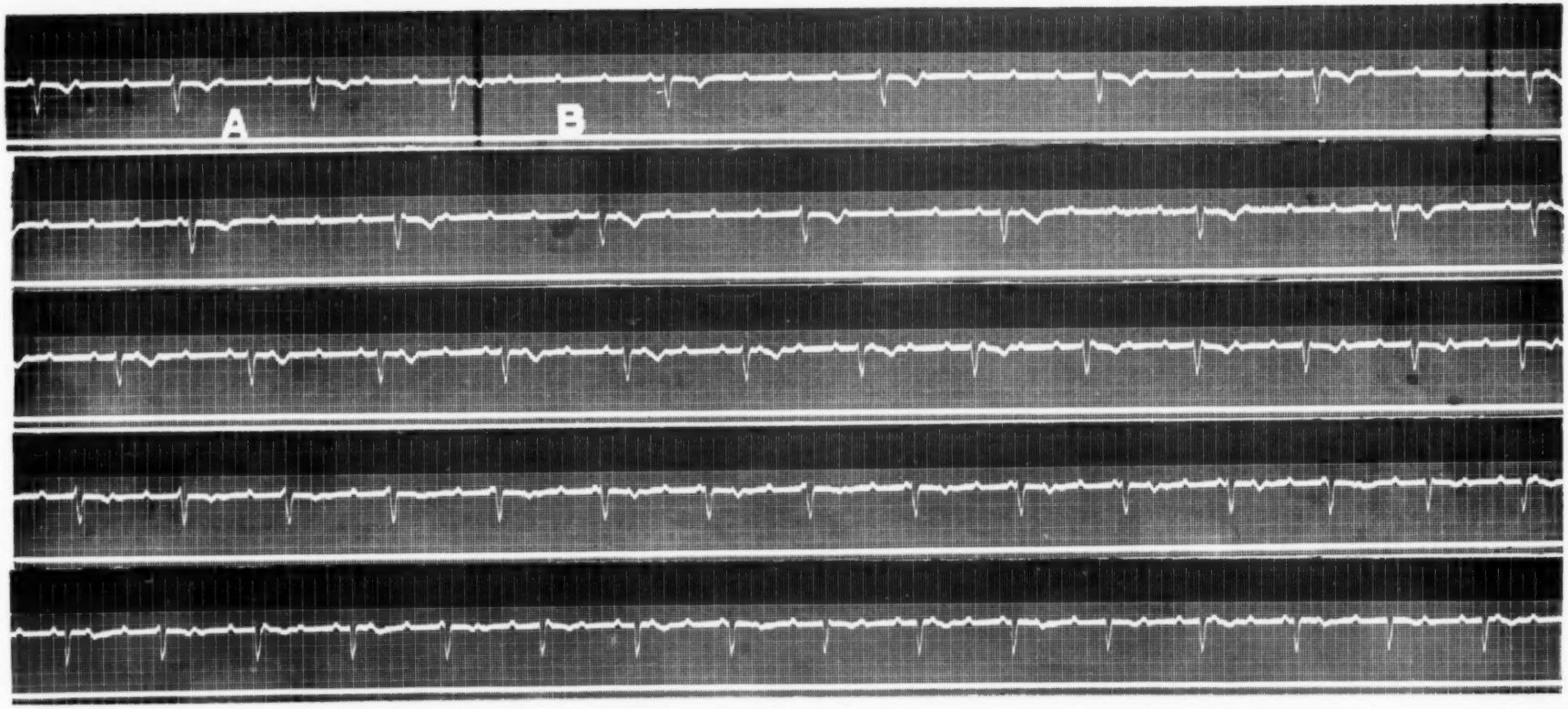

Fig. 4.—Atropine sulfate slows the idioventricular rate from an average of 27.2 beats (*A*) to 17.6 beats per minute, before causing a final acceleration to 39.4 beats (*C*) which lasts for forty-two minutes.

they arise from different foci than do the other beats with the downwardly directed ventricular complexes. They are not premature beats of the ventricles, since in an A-V dissociation, premature beats are usually associated with long compensatory pauses (Fig. 2,*G*).

5. Finally, another important change in rate and rhythm occurs during bodily rest when the idioventricular rhythm is governed by a ventricular complex that is totally different in shape, size, and form from the usual one in the same patient. (In Fig. 7,*A* compare the ventricular complexes in *A* with those of *D*.) These may be opposite in direction to the usual ventricular complexes; they may be markedly aberrant with prolonged RS-T segments and markedly negative T waves although the ventricular rate may average the same as the rate of the ventricles when the complexes are of the supraventricular form. At such times the auricular rate appears to remain the same.

Effects of Atropine Sulfate on the Idioventricular Rate and Rhythm During Bodily Rest

Since it has become customary to determine the vagal influences on the cardiac mechanism with atropine sulfate, the intravenous effects of the drug were studied in the presence of the numerous alterations in the idioventricular rate and rhythm that were observed during bodily rest.

The Initial Slowing Effects of Atropine on the Idioventricular Rate.—The earliest and first manifestation of the effects of atropine on the idioventricular pacemaker may consist of a *slowing* of the ventricular rate. For example, Fig. 4 was obtained at a time when the idioventricular rhythm was regular and no premature beats had been observed through the day. The ventricular rate averaged 27.2 beats per minute and the auricular rate was 87.4 beats. Immediately after the injection of atropine the auricular rate slowed to 75 beats per minute, the ventricles remaining at the original rate (Fig. 4,*A*). Eight and one-half seconds later (Fig. 4,*B*) there was an abrupt slowing of the ventricles to 17.6 beats per minute while the auricular rate increased to 83.3 beats. This lasted for 42.64 seconds before there was a progressive and gradual acceleration of the ventricular rate to 39.4 beats per minute while the auricles had increased to 100 beats (Fig. 4,*C*). This ventricular rate persisted for two hours and twelve minutes when it slowed to 26 beats per minute and for the next twenty-four hours this rate persisted without interruption. The auricular rate increased eventually to 115.7 beats in the first hour, but leveled to 85 beats four hours following the injection. The ventricular complexes remained the same from beat to beat throughout this experiment.

Such initial slowing of the ventricular rate preceding the usual transitory acceleration of the ventricles was obtained on several occasions on the same patient and also on different patients but not always to this extent. At times the ventricles slowed for only a few seconds and often this slowing occurred after some acceleration had taken place. The slowing was variable in its appearance and duration from time to time and no two patients were found to respond alike to the drug. Frequently no slowing of the ventricles appeared before the acceleration. The auricles also slowed initially but during the slowing of the ventricles the auricular rate increased as compared to the initial effects.

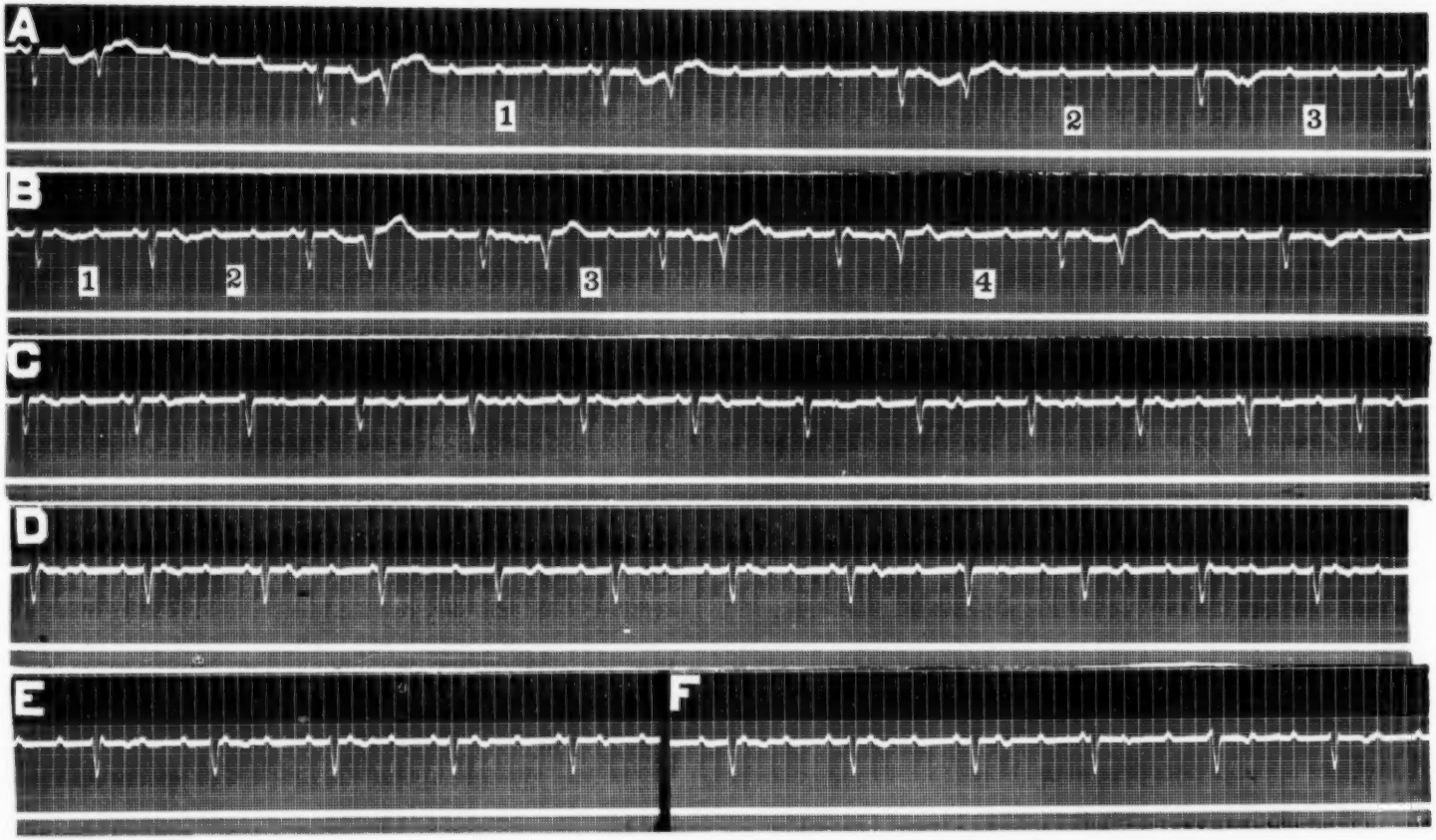

Fig. 5.—*A*, Control record, Lead II. The basic idioventricular rate averages 20.5 beats per minute (3). The sphygmic interval when premature beats are present measures 3.88 seconds (1) and 4.12 seconds (2) respectively. *B*, two and one-half minutes after the injection of atropine. The basic idioventricular rate now averages 27.7 and 38.4 beats per minute (1 and 2). The sphygmic interval in which premature beats are present now measures 2.32 seconds (3) and 30.4 seconds (4) respectively. *C*, Eight and one-half minutes after the injection of atropine. The idioventricular rate averages 38 and 39 beats per minute. *D*, *E*, and *F*, Progressive slowing of the idioventricular rate to 35.7 beats per minute, four and one-half hours after the injection of atropine.

The rate and rhythm of the ventricles prior to the injection of the atropine bore no relation to the subsequent slowing response of the idioventricular pacemaker. This slowing response, however, appeared much more readily when the cardiac mechanism was in a "labile" state rather than in a "relatively fixed" state.

It has been well known, since Anrep's[18] observations in 1880 and confirmed by others,[19] that the initial effect of atropine on the sinus rhythm was to slow the pulse rate; the late effect was to accelerate it. In the majority of instances this slowing was found to be a temporary effect of short duration although it has been reported that occasionally the slowing lasted for many hours.[20]

In a study of the oculocardiac reflex, Petzetakis[21] demonstrated that the slowing of the sinus rate produced by pressure over the eyeballs was accentuated in its early phases by the use of atropine. The late effects of the drug abolished the reflex. This slowing effect was attributed to an "increase in the excitability of the cardiac moderator elements contained in the vagi," while the later accelerating effects of the heart were attributed to paresis of the vagal endings.

McGuigan[22] attributed the sinus slowing to the dose of the drug. He obtained minimal or hardly any slowing with a dose of grain 1/30 whereas it was more noticeable when grain 1/100 or grain 1/120 was used.

This slowing response of the ventricles to atropine sulfate offers a clear explanation for the recurrent spontaneous periods of "slowing" of the idioventricular pacemaker that are observed in such patients during bodily rest. It is either a direct or reflex vagal effect through the carotid sinus. Unfortunately, attempts to reproduce such slowing of the ventricles by carotid sinus pressure or reflexly by changes in the blood pressure through the cold pressor tests or variations in respirations such as the Valsalva experiments, have been unsuccessful in these patients.

Effects of Atropine Sulfate on Premature Beats of the Ventricles in Patients With A-V Dissociation and Transient Periods of Ventricular Fibrillation.— Within recent date the suggestion has been made that atropine would appear to be of value in preventing ventricular tachycardia and perhaps terminal ventricular fibrillation in man. Atropine was found to abolish ventricular tachycardia induced in the dog by the intravenous injection of epinephrine.[23] Some have felt that the beneficial effects of atropine in lowering mortality of dogs following experimental coronary artery ligation was also in large part due to the influence of the drug in preventing ventricular tachycardia and ventricular fibrillation.[24]

Although the type of ventricular fibrillation during established A-V dissociation is not necessarily terminal in character, it was thought worth while to try atropine on patients with premature beats of the ventricles, since such isolated premature beats have invariably been found to be the forerunner of transient ventricular fibrillation. Furthermore, a comparison was made between the effects of atropine on such spontaneously developed premature beats and premature beats induced by the intramuscular injection of epinephrine.

Atropine sulfate was found to abolish spontaneously developing premature beats in certain patients with A-V dissociation, subject to transient periods of ventricular fibrillation. For example, in Fig. 5,*A* a control record reveals the

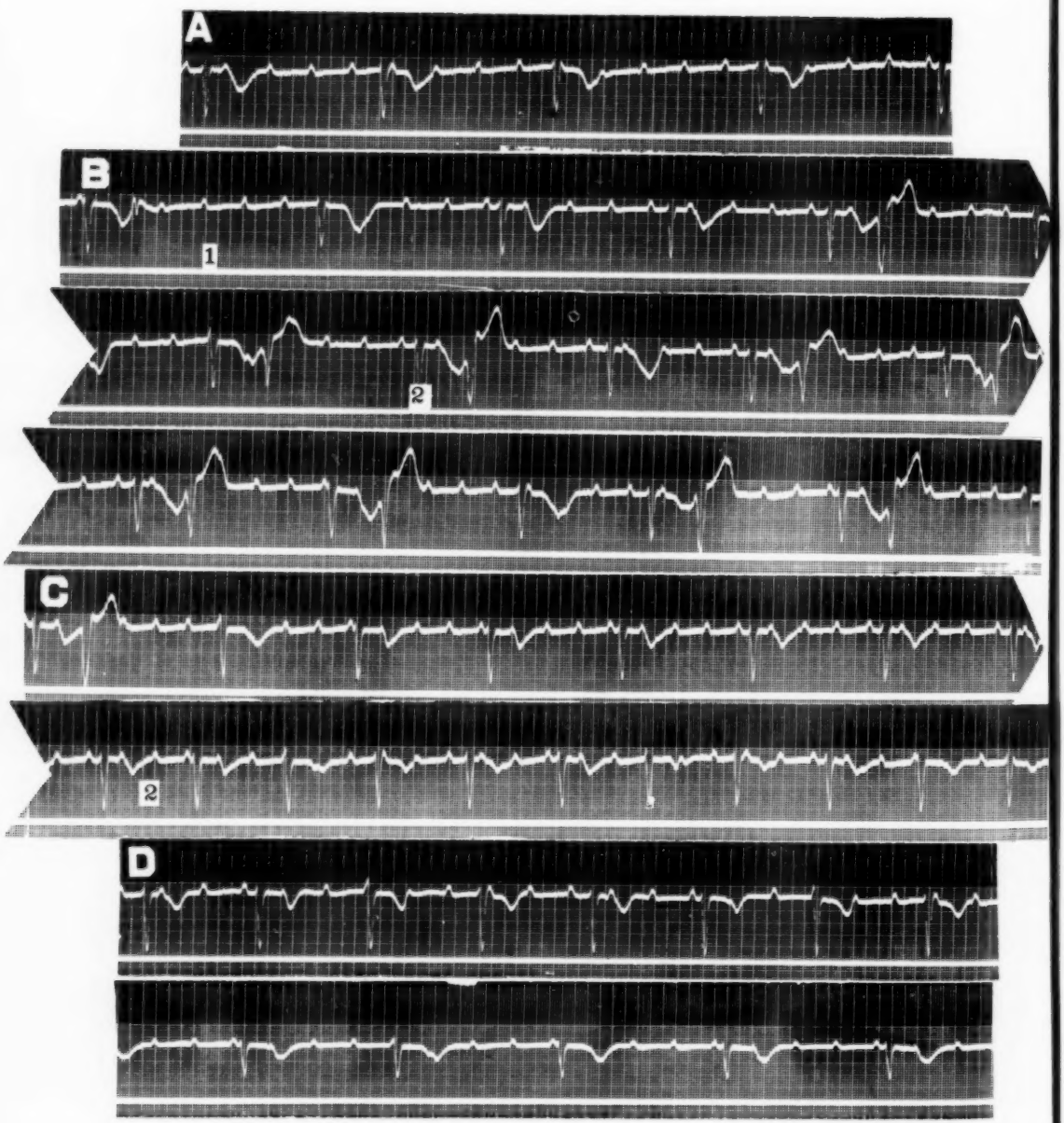

Fig. 6.—*A*, Control record, Lead II. The idioventricular rhythm is "labile." The sphygmic interval varies from 2.76 seconds to 3.32 seconds. The auricular rate averages 88.2 beats per minute. *B* (see also Table I), Atropine sulfate accelerates the idioventricular rate by reducing the sphygmic intervals from beat to beat and causes the premature beats to disappear within three seconds after the injection of the drug. The auricular rate increases to 115.3 beats per minute. *C*, Six and one-half seconds later the idioventricular rate averages 25 beats per minute (1) and increases to 40 beats within a few seconds. *D* and *E*, Fifty-five minutes after the injection of atropine the idioventricular rate averages 23.7 beats and the auricles average 88.2 beats per minute. All the premature beats of the ventricles have disappeared.

auricular rate to be 100 beats per minute and the ventricular rate averaged 20.5 beats independent of the presence of premature beats of the ventricles (Fig. 5,*A*[3]). The premature beats were constant and the patient was conscious of their presence in the form of "coupling." The sphygmic interval between two idioventricular beats measured 2.88 seconds as compared with 3.88 and 4.12 seconds when the premature beats were present (Fig. 5,*A*[1] and [2]). The distance between the premature beats and the idioventricular beat preceding it was 0.88 second and this was relatively stationary from beat to beat.

Two and one-half minutes after the injection of atropine the basic idioventricular rate was accelerated with an irregular rhythm that varied between 27.7 and 38.4 beats per minute independent of the premature beats (Fig. 5,*B*[1] and [2]). Although the distances between the basic ventricular complexes and the premature beats that followed these were the same as in the control records, the intersystolic interval in which the premature beats were present was now reduced from a minimum of 2.32 seconds to a maximum of 30.4 seconds respectively (Fig. 5,*B*[3] and [4]). This gave rise for a short period to a totally irregular rhythm that lasted four and one-half minutes. Eight and one-half minutes after the injection of atropine the ventricular rate rose to between 38 and 39 beats per minute (Fig. 5,*C*), and became perfectly regular when the premature beats disappeared entirely.

For the ensuing twenty-four hours the patient was no longer conscious of "coupled" beats and repeated electrocardiograms obtained through this period revealed a ventricular rate of 35.7 beats as long as four hours after the injection of the atropine (Fig. 5,*F*). The ventricular rate gradually returned to 24 beats per minute and the premature beats did not recur for twenty-six hours.

It was possible to prevent the appearance of premature beats in this patient by the daily administration of atropine (grain 1/100) intramuscularly. Indeed, he found the drug so beneficial in the avoidance of symptoms associated with "coupling" that he was encouraged to use it whenever he felt its need. If the atropine was omitted for twenty-four hours the premature beats returned.

Another experiment was carried out on the same patient at a time when he complained of "coupling" of his heart beats which appeared at recurrent intervals and was inconstant in its duration from hour to hour.

A control record obtained at an interval when coupling was not present revealed a slightly irregular rhythm of the idioventricular beats with sphygmic intervals varying between 2.76 and 3.32 seconds (Fig. 6,*A*). The auricular rate averaged 88.2 beats per minute.

A few minutes later, after the appearance of coupling due to the presence of alternate premature beats of the ventricles, and when the patient was conscious of his heart beating irregularly, atropine (grain 1/30) was given intravenously. A continuous strip of the electrocardiogram (Fig. 6,*B*), obtained three seconds after the injection of the drug, revealed a progressive reduction in the sphygmic interval from beat to beat from 2.96 to 2.16 seconds in the absence of any premature beats of the ventricles (Table I). Simultaneously with the acceleration of the idioventricular rate there was a gradual decrease in this intersystolic interval in which the premature beat was present from 3.80 to 3.12

seconds. In the meantime the auricles increased in rate from 88.2 beats per minute to 115.3 beats toward the end of this interval. (In Fig. 6,*B*, compare the rate of the auricles at 1 with those at 2.)

TABLE I. PROGRESSIVE DECREASE IN SPHYGMIC INTERVALS AFTER INJECTION OF ATROPINE SULFATE*

NUMBER OF SPHYGMIC INTERVAL	DURATION OF INTERVAL WITHOUT PREMATURE BEATS (SECONDS)	DURATION OF INTERVAL WITH PREMATURE BEATS (SECONDS)
1		3.80
2	2.96	
3	2.76	
4	2.60	
5		3.86
6	2.48	
7		3.40
8		3.12
9	2.32	
10		3.20
11		3.04
12		3.20
13		3.08
14	2.16	
15		3.12
16		3.16

*This table corresponds to Fig. 6, *B*.

Six and one-half seconds later the auricular rate was the same, but the ventricles now averaged 25 beats per minute, their rhythm was regular, and the last of the premature beats of the ventricles was registered in the electrocardiogram (Fig. 6,*C*[1]). A sudden and further acceleration of the ventricles ensued (Fig. 6,*C*[2]) so that the rate was now 40 beats per minute and the rhythm was almost perfectly regular and remained so although the ventricular rate slowed progressively to 33 beats per minute, exactly forty-five minutes after the injection of the atropine. Ten minutes later the heart rate averaged 23.7 beats per minute and the auricular rate returned to its original level of 88.2 beats. For the ensuing twenty-four hours the patient was perfectly comfortable and showed no coupling.

These effects of atropine in abolishing the premature beats of the ventricles suggest the possibility that these spontaneous premature beats may represent a vagal effect or one associated with reflex changes in the carotid sinus. Hering[25] has brought forth some experimental proof for such a possibility in the lower mammalian heart. Since these premature beats disappeared simultaneously with the increase in the idioventricular rate after the injection of atropine, their abolition might be attributed to this increase in rate. However, atropine failed to abolish in such patients premature beats induced with epinephrine, although the idioventricular pacemaker was accelerated to an even higher rate.[17]

It is much more likely that atropine acts on the acetylcholine-cholinesterase mechanism to prevent reflex vagal-induced premature beats of the ventricles and perhaps in this way the onset of transient seizures of ventricular fibrillation are

avoided.[23] Further evidence in support of this contention may be gained from the fact that atropine can abolish intraventricular conduction disturbances which may be of vagal origin without changes in the idioventricular rate.

Effects of Atropine Sulfate on the Idioventricular Pacemaker Arising in a Bundle.—One of the characteristic features of the idioventricular pacemaker in

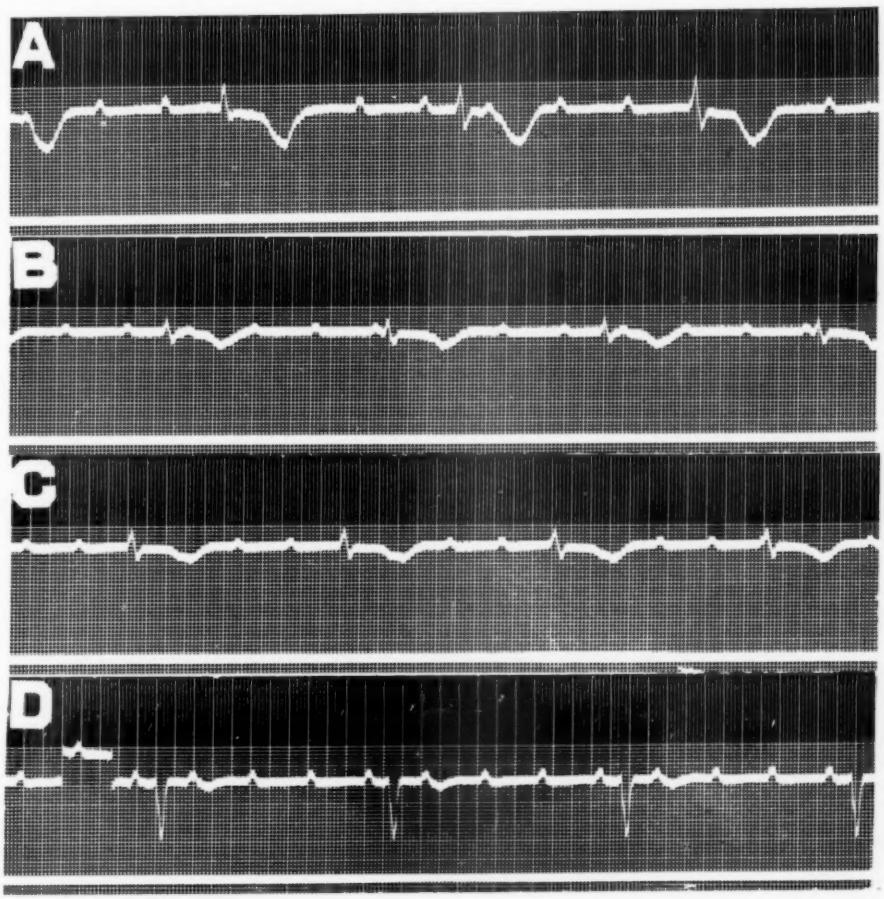

Fig. 7.—*A*, Atropine sulfate may influence the idioventricular pacemaker of the heart without changing the idioventricular rate. The idioventricular rate is governed by a beat with an aberrant upwardly directed ventricular complex which has a prolonged RS-T segment and a markedly negative T wave, 10 mm. in depth. *B*, Sixteen seconds after the injection of atropine the height of the QRS complex and the T waves are diminished. *C*, A further reduction in the QRS complex and T segments ensues three minutes and ten seconds later. The auricular rate remains unchanged. *D*, There follows a sudden change to the basic idioventricular rhythm with normal complexes, twenty seconds later.

patients with transient ventricular fibrillation during established A-V dissociation is the periodic alternation of the basic mechanism, with supraventricular complexes which presumably arise in the A-V node and an idioventricular pacemaker that arises in one of the bundles as indicated by the ventricular complexes which have prolonged RS-T segments and markedly inverted T waves. This type of mechanism is particularly noticeable prior to the onset of transient

periods of ventricular fibrillation. The ventricular rate during the presence of this type of complex may be slower or the same rate as that governed by the supraventricular complex. In Fig. 7,*A* the A-V rhythm is governed by a beat with an upwardly directed aberrant ventricular complex that has a prolonged RS-T segment and a markedly negative T wave almost 10 mm. in depth. The auricular rate is 88.2 beats per minute and the ventricular rate is 25 beats. Sixteen seconds after the injection of atropine the height of the ventricular complexes is reduced by almost one half and, although the RS-T segment is of the same duration, the negative T is now only 4 mm. in depth. The auricles remain at the same rate but the ventricles have increased slightly to 26.3 (Fig. 7,*B*).

A further reduction in the size of the negative T wave was noted three minutes and ten seconds later (Fig. 7,*C*). Twenty seconds after this event the supraventricular complexes reappeared with a ventricular rate of only 28.3 and an auricular rate of 93.8 (Fig. 7,*D*). That this radical change in the cardiac mechanism was due to atropine with hardly any changes in the idioventricular rate may be deduced from the progressive diminution of the RS-T segments and T waves accompanying the main ventricular deflections.

EFFECTS OF EXERCISE ON THE IDIOVENTRICULAR RATE AND RHYTHM IN PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION DURING ESTABLISHED A-V DISSOCIATION

There is now sufficient evidence that muscular exertion will increase the idioventricular rate during A-V dissociation.[11] The increase is immediate and the ventricular rate has to be counted continuously for every few seconds; otherwise the effects wear off within one or two minutes and may be missed entirely. In two of our patients, who were bedridden, bending the body trunk backward and forward accelerated the ventricles from an average of 24.2 and 28.4 beats per minute to 34.5 and 32.4 beats respectively. In both instances the idioventricular rate returned to a basic level in less than one minute.

In one patient, however, the effects of various types of exertion yielded unusual manifestations which deserve a detailed analysis.

Transitory Slowing of the Idioventricular Rate Following Exertion.—The effects of muscular exertion while reclining in bed and lifting weights attached by a pulley system to the right leg were noted at a time when the idioventricular pacemaker was very labile. In Fig. 8, *A* to *D* represent portions of records obtained during bodily rest before the exercise test. Although the auricular rate averaged 100 beats per minute and is constant from record to record, the ventricular rate varied from moment to moment. In Fig. 8,*A* the ventricles averaged 27.2 beats per minute; in Fig. 8,*B*, obtained a few minutes later, the ventricles changed to an average of 28 beats; in Fig. 8,*D* they average 32.8 beats. Fig. 8,*E* is a record obtained during exercise such as may be gained from the presence of somatic tremors. The ventricular rate averages 37.5 beats per minute. Immediately after exercise, however, instead of a further acceleration as was to be expected from other similar experiences, there is a definite *slowing* of the idioventricular rate to an average of 25.8 beats per minute (Fig. 8,*F*).

This postexertional slowing is associated with a slight but definite change in the ventricular complexes which now reveal a prolongation of the RS-T segment with a more pronounced negativity of the T wave as compared with the records obtained when the patient was at bodily rest. In other words, a distinct depression of conduction within the ventricles resulted from this type of mild exertion.

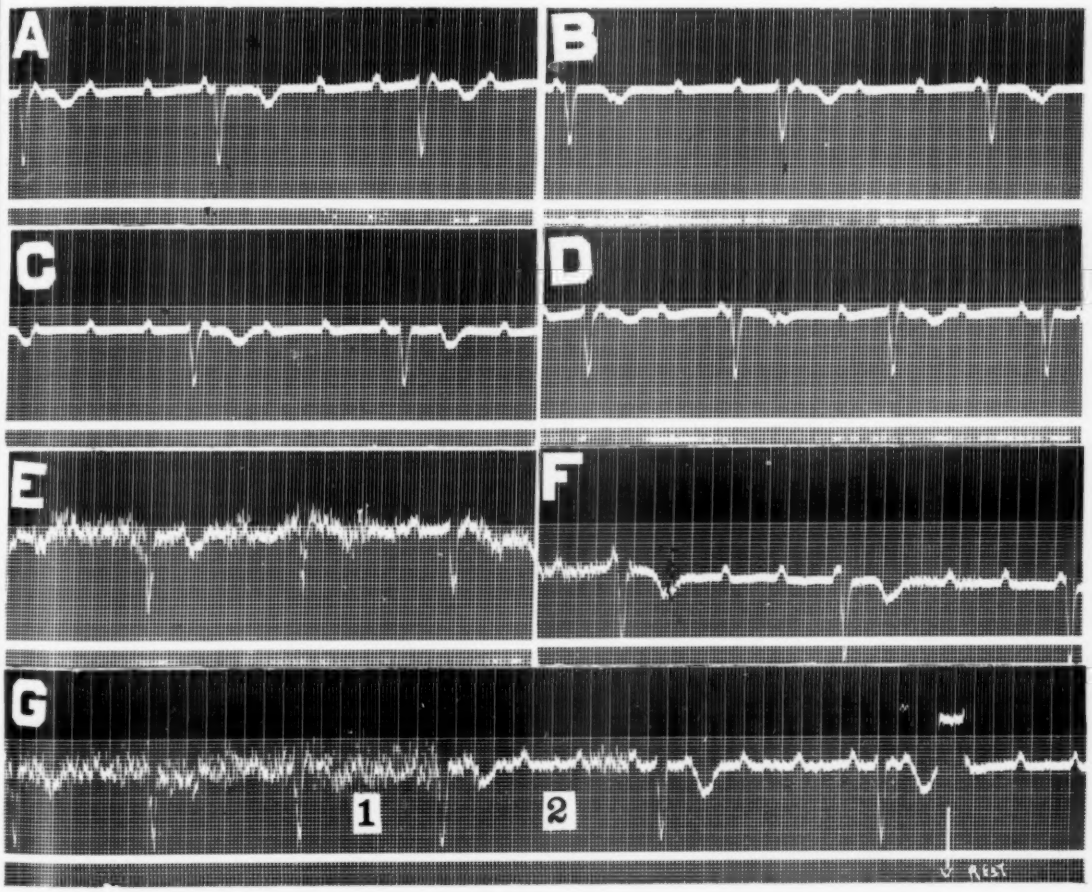

Fig. 8.—Mild exertion may cause a transitory slowing of the idioventricular rate immediately after cessation of muscular activity. *A*, *B*, *C*, and *D*, These records show a labile idioventricular rate varying from 27.2 beats per minute (*A*) to 32.8 beats per minute (*D*) before exertion accelerates the ventricular rate to 37.5 beats per minute (*E*) during muscular activity. Immediately after the exertion period, the idioventricular rate slows to 25.8 beats per minute. *F*, Exertion accelerates the idioventricular rate to 35.7 beats (1) and this is abruptly lowered to 26.3 beats (2) on cessation of muscular activity.

The immediate effects of another similar experiment, depicted in Fig. 8,*G*(1), demonstrated that during muscular activity such as may be gained from the somatic tremors in the record the ventricular rate averages 35.7 beats per minute and is immediately lowered to 26.3 beats per minute (Fig. 8,*G*[2]) as the muscular activity ceases. Since this type of exertion was not marked, in both experiments the auricular rate did not change at all. It averaged 100 beats before and immediately after the experiments.

The changes following exertion to the point of fatigue were more marked and the transitory slowing lasted longer. For example, in Fig. 9,*A* the rate of the idioventricular pacemaker before exercise, while the patient was standing still, was 33.3 beats while the auricles averaged 100 beats. No record was obtained during the exercise itself but immediately following it, although the

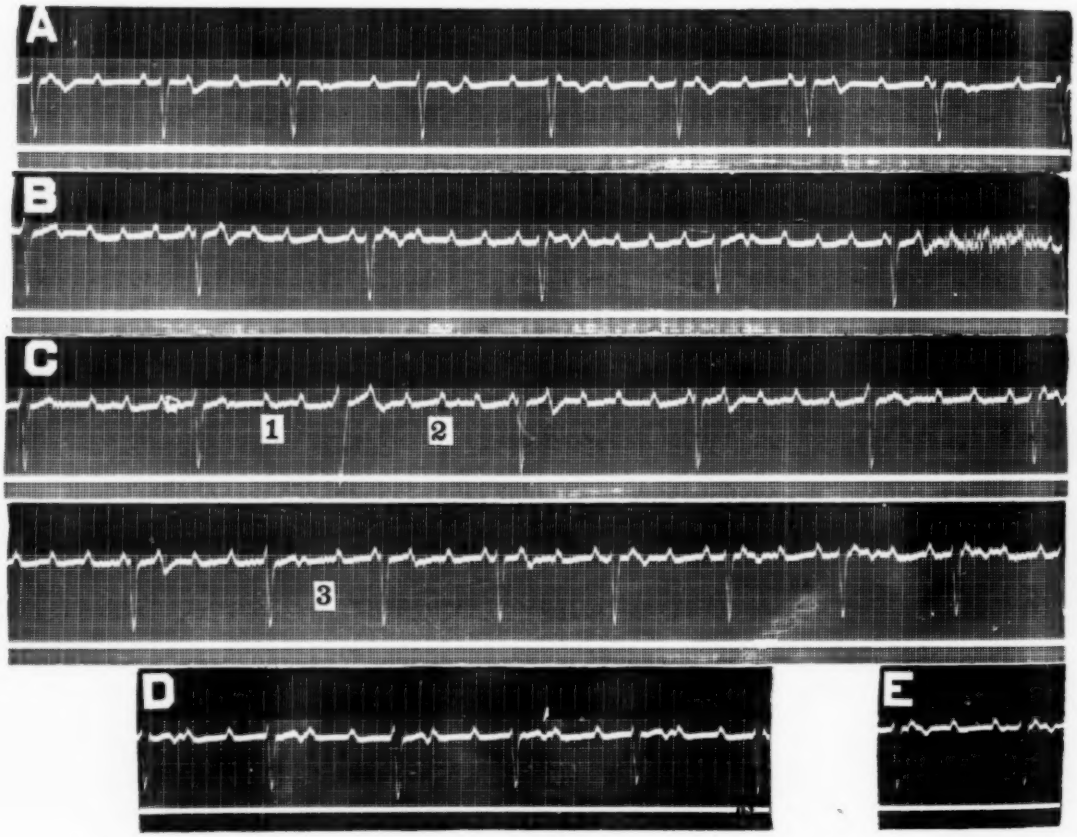

Fig. 9.—Exertion to the point of fatigue may cause a transitory slowing of the idioventricular rate. *A*, In the control record the idioventricular rate averages 33.3 beats per minute and the auricles average 100 beats. *B*, Immediately after exertion the ventricle slowed to 25.4 beats while the auricles increased to 125 beats. *C*, Fifteen seconds later the ventricles gradually increased in rate to 38.5 beats (3) after developing an irregular rhythm (1 and 2). The idioventricular rate then gradually slowed to to 34 (*D*) and 33.3 (*E*) beats within one minute and forty seconds.

auricular rate was accelerated to 125 beats per minute, the ventricles were slowed to 25.4 beats (Fig. 9,*B*). Within 15 seconds there appeared a periodic irregularity in the sphygmic interval in which one interval measuring 2.0 seconds (Fig. 9,*C*[1]) alternated with another measuring 2.62 seconds (Fig. 9,*C*[2]) before the ventricular rate was suddenly accelerated to 38.5 beats per minute (Fig. 9,*C*[3]) although the auricles now slowed to 100 beats. Following this increase in ventricular rate there then ensued a gradual slowing of the ventricles to 34 beats (Fig. 9,*D*) and finally to 33.3 beats (Fig. 9,*E*) within a minute and forty seconds after the exercise.

The effects of exercise to the point of fatigue were essayed on another day when the patient complained of periodic pauses in his heart beat. He was extremely conscious of the forceful beating that followed these long pauses, which averaged 4.2 seconds in duration (Fig. 10,*A*[1]), and recurred quite often, alternating with a regular ventricular rate averaging 30 beats per minute (Fig. 1,*A*[2]). The auricles averaged 100 beats.

Fifteen seconds after the beginning of exercise the ventricular rate increased to 38 beats per minute and the pulse pauses disappeared. The exertion to the point of fatigue did not accelerate the ventricles any further at this time. No records were taken during the exercise.

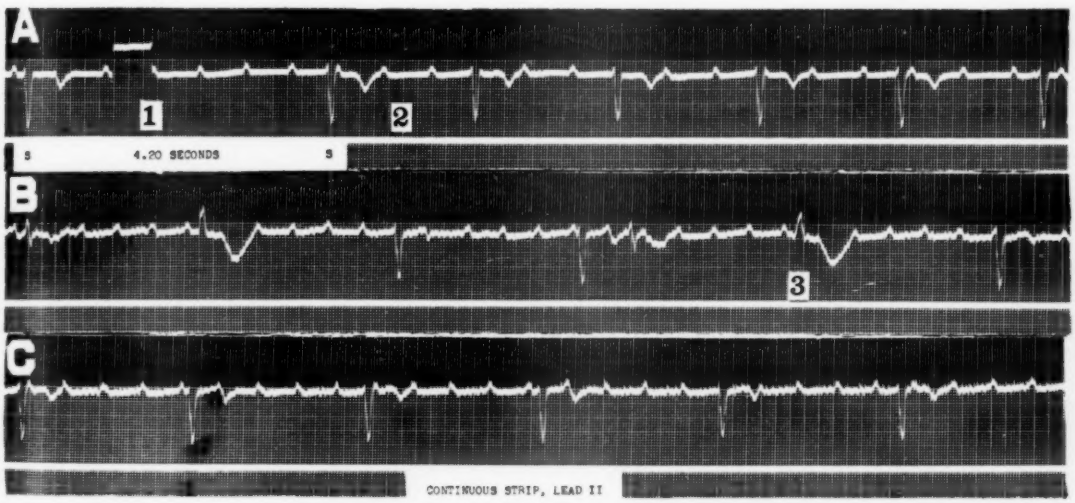

Fig. 10.—Exertion to fatigue may change the pacemaker of the heart from a supraventricular focus in the A-V node to a focus in one of the bundles. *A*, Control record. The idioventricular rate averages 30 beats per minute (2) with interruptions of long pauses measuring 4.2 seconds (1). *B*, Following exertion there appears a new center of impulse formation in one of the bundles (3) with a transitory slowing of the idioventricular rate and the appearance of premature beats of the ventricles. *C*, Fifteen seconds later the idioventricular rate increased again to 24.2 beats.

Immediately after the cessation of the exercise the electrocardiogram revealed an acceleration of the auricular rate to 125 beats per minute. The idioventricular rhythm, however, became irregular and *slower*. The irregularity was due to: (1) an increase in the sphygmic interval of the basic ventricular beats in which the ventricular complexes resembled those before the exercise was initiated (Fig. 10,*B*[1]), (2) the development of premature beats of the ventricles that invariably followed the basic ventricular complex (Fig. 10,*B*[2]), and (3) the change in the pacemaker of these idioventricular beats from the A-V node to one of the bundles (Fig. 10,*B*[3]). This is characterized in the record by the appearance of aberrant ventricular complexes with prolonged RS-T segments and markedly inverted large T waves. The sphygmic interval between one of these aberrant beats and a basic ventricular complex measured 2.80 seconds; the sphygmic interval between two basic ventricular beats measured

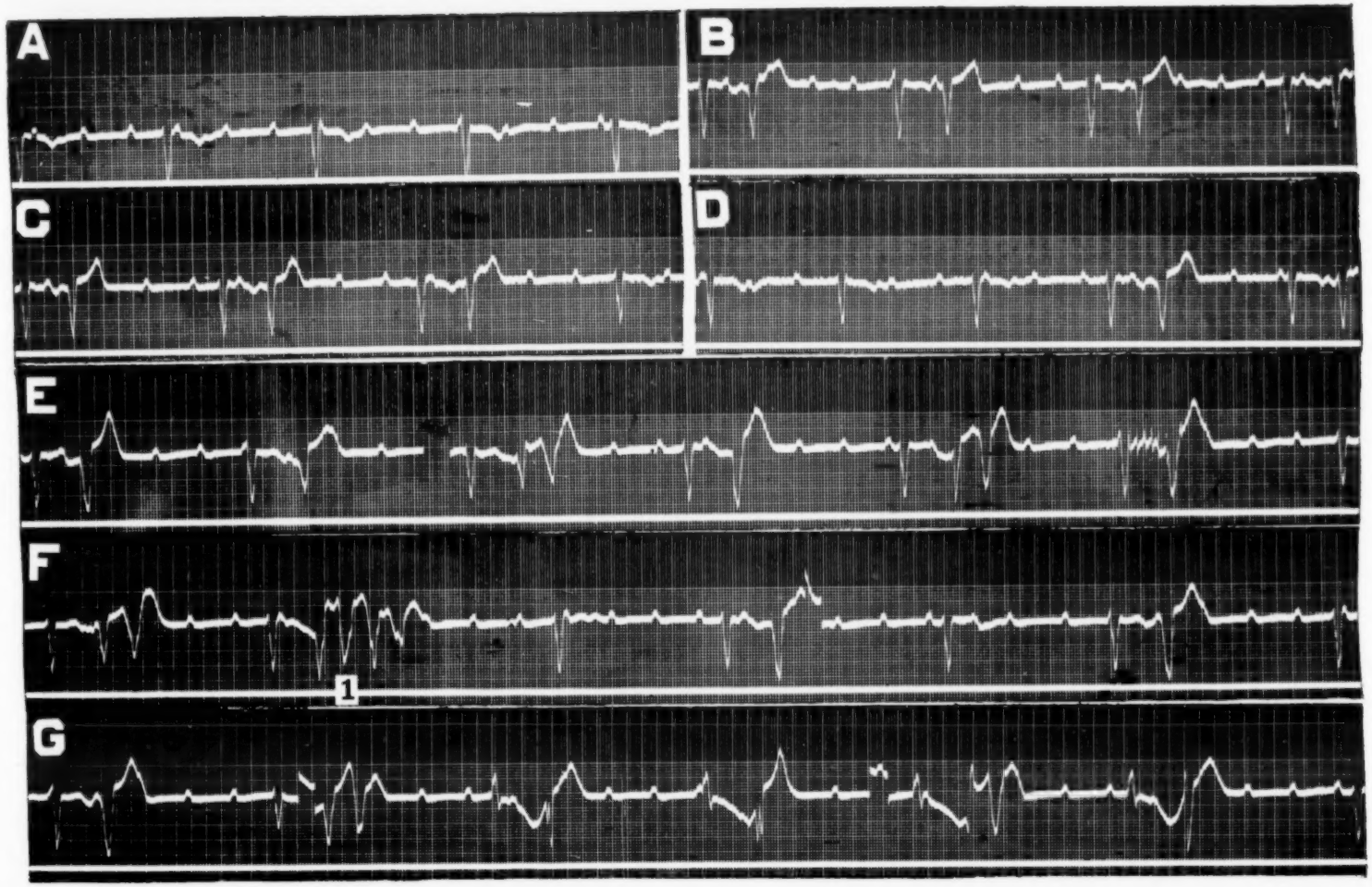

Fig. 11.—Exertion to the point of fatigue may precipitate transient ventricular fibrillation. *A*, **Control record.** *B*, **Immediately after exertion premature beats of the ventricle appear.** *C*, *D*, **and** *E*, **These increase in frequency and persist until finally there appear (*F* [1]) short runs of ventricular fibrillation, one and one-half hours after the onset of the experiment.** *G*, **Deformed ventricular complexes forming the prefibrillatory period of longer seizures appear after these.**

2.52 seconds while the interval between the sphygmic intervals during the presence of the premature beat of the ventricles measured 2.96 seconds. The aberrant ventricular complex reappeared only following the premature beat of the ventricles.

Approximately fifteen seconds later the ventricular rate became regular again and averaged 24.2 beats. It did not return to the original level of 30 beats until about two and one-half minutes had elapsed although the auricular rate slowed to 100 beats per minute (Fig. 10,*C*).

It is of more than academic interest to speculate on some of the factors which cause this transitory slowing of the idioventricular rate during A-V dissociation in patients with transient ventricular fibrillation, for this "paradoxical" mechanism may well be responsible for many of the syncopal seizures associated with transient periods of ventricular fibrillation following exertion in these patients.

Since exertion is usually associated with an increase in the systemic blood pressure the most likely cause for this transitory slowing of the idioventricular rate would be naturally attributed to the increased pressure. With the tone of the vagus nerves dependent in part upon the intra-aortic and carotid artery pressures, it is fair to assume that the increase in blood pressure following exertion reflexly increases the tone of the vagus and tends to lower the tones of the cardio-accelerator nerves.[26] This slowing should be enhanced in a patient with a sensitive aortic carotid sinus system and the whole phenomenon of slowing should be abolished in its entirety by atropine sulfate which would obviously accelerate the ventricles and thus prevent the slowing. Unfortunately, such is not the result in every instance of A-V dissociation nor has it at times in the same patient, been possible to obviate the slowing with atropine no matter how large the dose. Atropine, as has been pointed out previously, has an initial transitory slowing effect on the auricles. Exercise and atropine together not only abolish this slowing reflex but accelerate the auricular rate. In the presence of established A-V dissociation this acceleration of the auricles may increase the A-V block[27] and thus slowing of the idioventricular rate may ensue despite the use of atropine.

Immediate Development of Premature Beats of the Ventricles Following Exertion.—In the patient of the preceding experiment, on another occasion, exertion to the point of fatigue, following a period of rest, revealed a different type of mechanism from those previously described.

With the patient in a sitting posture the control ventricular rate was 30.6 beats per minute and the auricles averaged 100 beats (Fig. 11,*A*). Immediately after bending the body backward and forward the auricles increased to 107 beats per minute and there developed "coupling" due to the presence of alternate premature beats of the ventricles (Fig. 11,*B*).

One-half minute later the auricles slowed to 88.2 beats but the bigeminal rhythm due to the alternate premature beats of the ventricles persisted (Fig. 11,*C*). A further slowing of the auricular rate to 83 beats per minute was recorded two minutes later; the idioventricular rate was recorded two minutes ater at 33.3 beats per minute with the premature beats still persisting (Fig. 11,*D*).

One hour and ten minutes later there was an increase in the recurring number of premature beats of the ventricles so that now a bigeminal rhythm alternated with a trigeminal rhythm owing to two premature beats of the ventricles that followed the idioventricular beat (Fig. 11,*E*). At this time, all of the premature beats were audible at the apical region of the heart and their pulses were palpable at the wrist.

However, within twenty minutes, that is, one and one-half hours after the beginning of the experiment, short runs of ventricular fibrillation appeared (Fig. 11,*F*). The auricular rate was 100 beats per minute. The basic indioventricular rate had slowed to 26.8 beats, but now only the first of the premature beats of the ventricles which followed the indioventricular beat was audible at the apical region of the heart and its pulse could be felt at the wrist. After the first premature beat there followed clinical pulse pauses, which in their final analyses in the electrocardiogram are short runs of ventricular fibrillation (Fig. 11,*F*[1]).

Fifteen minutes later there appeared deformed ventricular comlexes with an aberrant idioventricular beat, a phenomenon which has been found invariably to be the forerunner of longer periods of transient ventricular fibrillation.

DISCUSSION

These observations reveal that in patients subject to transient seizures of ventricular fibrillation in the presence of established A-V dissociation the idioventricular pacemaker is at all times under the influence of the extrinsic nerves of the heart. There are periods, however, when the pacemaker is more "labile" in its reaction and it is at such times that the most marked changes may be observed both in vagal and in accelerator effects.

Because of these variations it is not difficult, with the knowledge at hand, to reconcile the unusual alternate slowing and acceleration of the ventricular rate during bodily rest or in the wake of emotional disturbances with the occasional development of transient ventricular fibrillation which may occur even during deep sleep. It would appear that this ability of the idioventricular pacemaker to accelerate its rate in a matter of seconds may, under certain conditions, favor the development of a depression of conduction within the ventricles. This may be seen from the changes wrought in the prolonged RS-T segments and the progressively negative T waves as the earliest phases following this hastening of the ventricles. Again such alternate acceleration and retardation of the idioventricular pacemaker may, after a certain period of this type of mechanism, fatigue the node and yield its impulse-originating center to one of the bundles. In the presence of such marked conduction disturbances as is evidenced by the newly aberrant ventricular complexes, there is a tendency for the heart to develop premature beats of the ventricles whose recurrent presence further enhances depression of conduction within the ventricles.

In a minority of these cases the impetus for the onset of these premature beats may be vagal in origin or result from reflexes originating in the carotid sinus, for atropine abolished these very readily. In others the presence of A-V dissociation with conduction disturbances in the ventricles favors the development of

ectopic foci more readily than the presence of normal sinus rhythm. Clerc and Levy[28] have called attention to the ease with which the heart in A-V dissociation can tolerate these changes although as yet an adequate explanation for this peculiarity is still wanting.

If the premature beats are not of vagal or carotid sinus origin, then atropine sulfate does not abolish them. Their continued presence may enhance intraventricular conduction disturbances and in this way facilitate a shortening of the refractory period within the ventricles. Hence the heart is conditioned to a circus movement and is in readiness for the "initial" stimulus following the appearance of premature beats, for without this stimulus there cannot result any fibrillation of the ventricles in heart block. It is likely that asphyxial states in the already depressed heart muscle arising from the diminished ventricular output in the course of recurrent premature beats may be one of the most important factors.[29]

Such phenomenon may be observed at times in such patients particularly after undue forms of exertion. In one group, exertion may be associated with a "paradoxical" action of the ventricles. Exertion may slow the idioventricular rate, change the pacemaker of the heart from the A-V node to one of the bundles, and cause the appearance of premature beats of the ventricles and thus facilitate the shortening of the refractory period that would favor the development of ventricular fibrillation. In this group, atropine sulfate abolishes the slowing of the ventricles and thus prevents the onset of the fibrillary process, indicating again that the phenomenon may be of vagal or carotid sinus origin.

Under other circumstances, when the idioventricular pacemaker is not so "labile" but more "relatively fixed," in the same patient exertion may produce another type of mechanism that is refractory to atropine sulfate. It is very likely that the trend of signs that appear after exertion at such times is due solely to the accelerator mechanism and the vagal or aorticocarotid sinus mechanisms play no part at all. It is these patients that form the larger group of individuals with transient ventricular fibrillation in the presence of A-V dissociation who require further study for the relief of their symptoms and signs.

Since, as has been pointed out, the vagus and the carotid sinus play such an important part in the preliminary disturbances that lead to the development of transient ventricular fibrillation during A-V dissociation, digitalis bodies and quinidine sulfate are of little value in preventing the appearance of these alterations in rate and rhythm. Both of these drugs enhance the depressing action of the vagus upon the myocardium and thus facilitate the appearance of depressed conduction and its sequelae[30,31] with the development of transient ventricular fibrillation.

SUMMARY AND CONCLUSIONS

1. A study was made of the effects of bodily rest, atropine sulfate, and exercise on three patients with transient ventricular fibrillation during established A-V dissociation.

2. Two distinct mechanisms were found to exist in the idioventricular pacemaker during bodily rest. In one type the idioventricular rate was "relatively" fixed and did not vary more than eight beats per minute during the waking hours or during deep sleep. The second mechanism consisted of an unusually "labile" variation in the idioventricular rate and rhythm.

3. The idioventricular rate and rhythm during the presence of the "labile" mechanism changed remarkably from moment to moment. There appeared: (1) a progressive acceleration and slowing of the ventricles from as low a range as 14.2 beats per minute to 37.5 beats within a few seconds; (2) abrupt and sudden changes of alternating retardation and acceleration of the ventricular rate in which the ventricular complexes in the electrocardiogram were all of the supraventricular form and of the same size, shape, and direction from beat to beat; (3) premature beats of the ventricles; and, finally, (4) changes in the site of the idioventricular pacemaker from a supraventricular portion of the A-V node to one of the bundles, with ventricular complexes that were aberrant, and with prolonged RS-T segments and markedly negative T waves.

4. The intravenous administration of atropine sulfate (grain 1/30) resulted in: (1) a transitory slowing followed by (2) a transitory acceleration of the idioventricular rate; (3) the disappearance of the spontaneously developing premature beats of the ventricles, and (4) changes in the site of the idioventricular pacemaker from one of the bundles to the supraventricular portion of the A-V node, and finally (5) the disappearance of RS-T segment and T wave changes from negative to positive deflections.

5. The action of atropine sulfate in abolishing these spontaneously developing mechanisms leaves no doubt that the idioventricular pacemaker is at all times under the influence of vagus nerves or the carotid sinus mechanism, but more so during the presence of the "labile" mechanism involving the idioventricular node.

6. The daily use of atropine sulfate intramuscularly in doses of grain 1/100 was sufficient to prevent the lability of the idioventricular pacemaker and the appearance of premature beats of the ventricles in one patient with transient ventricular fibrillation during established A-V dissociation. In this manner it was possible to avoid the onset of transient seizures in this patient.

7. In two patients with transient fibrillation who were bedridden, mild exercise resulted in transient acceleration of the ventricles which disappeared entirely within a few minutes.

8. In one patient with transient ventricular fibrillation during established A-V dissociation, exercise resulted in: (1) a transitory slowing of the idioventricular rate and the presence of acceleration of the auricular rate, (2) a periodic and recurrent change in the site of the idioventricular pacemaker of the heart from a supraventricular portion of the A-V node to one of the bundles, and (3) the development of premature beats of the ventricles.

9. By increasing the systemic blood pressure, exertion reflexly slowed the idioventricular pacemaker through the vagus or carotid sinus mechanism. However, atropine sulfate and exertion combined accelerated the auricular rate.

This type of acceleration of the auricles increased the existing block. Consequently, atropine sulfate was of no value in preventing the appearance of alterations in the rhythm of the heart in such patients following exertion.

10. In one patient, exertion to the point of fatigue resulted in the immediate appearance of premature beats of the ventricles. The recurrent presence of these beats for over one hour after exertion further enhanced conduction disturbance within the ventricles so that a prefibrillatory period developed.

11. Since such alterations in the electrocardiogram have been found to be the forerunner of transient periods of ventricular fibrillation during established A-V dissociation, exertion may be said to be one of the factors in the development of transient periods of ventricular fibrillation.

12. The alterations in the idioventricular rate and rhythm that precede transient ventricular fibrillation in patients with established A-V dissociation are in great measure dependent upon the effects of the extrinsic nerves on the idioventricular pacemaker of the heart during bodily rest as well as during exertion.

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RELATIONSHIP BETWEEN THE INTRINSIC DEFLECTION AND SUBEPICARDIAL ACTIVATION

An Experimental Study

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THE term intrinsic deflection was created by Lewis[1] when he studied the potential variations in the auricular muscle by means of bipolar leads. The author said in this connection, " . . . when the electrodes are placed in the muscle of the auricle they produce deflections of two kinds. The chief deflections are those which result from the arrival of the excitation process immediately beneath the contacts; these I term intrinsic. They are deflections which represent relatively large electrical potentials and they have correspondingly large amplitudes. The deflections of the second order are those yielded by the activation of muscle lying at a distance from the actual contact points. These I qualify by the adjective extrinsic."

In unipolar leads registered at the epicardial surface, the intrinsic deflection is the rapidly inscribed line that goes from the point of greatest positivity to the one with greatest negativity if there is an S wave, or to the isoelectric line if there is not an S wave. In the majority of tracings it takes 0.01 to 0.02 second for the intrinsic deflection to be inscribed. In a few it may take 0.03 to 0.04 second. For these reasons, there may be differences of 0.02 second or more between the beginning and the end of the deflection. Thus, it seems logical to ask what portion of the intrinsic deflection shows us when the muscle in contact with the electrode is activated.

Routinely, we call the time of the appearance of the intrinsic deflection that time interval which elapses between the beginning of the ventricular complex and the highest part of the deflection. This measurement has proved to be of great value in the diagnosis of ventricular hypertrophy, of bundle branch block, and even of valvular lesions such as aortic insufficiency[2] and tricuspid lesions,[3] but it is evident that the highest point of the deflection corresponds to frank positivity (maximal in the majority of cases) of the muscle in contact with the exploring electrode, that is to say, muscle which has not yet been activated. A portion of muscle is made negative when it is activated and it is then a sink of current of all the regions that have not been activated.

Recently, Wilson[4] suggested that, in precordial and unipolar direct leads, the arrival of the excitation at the subepicardial muscle corresponds to the lowest point of the intrinsic deflection. Nevertheless, he has previously always used the upper part of the intrinsic deflection for the interpretation of his ordinary and experimental tracings.

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This paper was planned in order to determine what point of the intrinsic deflection corresponds to the arrival of the excitation wave at the subepicardial muscle fibers.

MATERIAL AND METHOD

Dogs weighing 10 to 20 kilograms were used. They were anesthetized with Dial (Ciba) injected into the peritoneum in the dose of 0.7 c.c. per kilogram of body weight, or with a mixture of a 20 per cent solution of Nembutal and 25 per cent urethane in the dose of 1.0 c.c. per 3.0 kilograms of body weight. Under complete anesthesia and after tracheal intubation for artificial respiration, the thoracic cavity was opened. The pericardium was cut lengthwise, sewed to the chest wall, and the anterior aspect of the heart exposed.

Unipolar and bipolar epicardial leads were used. The corresponding tracings were registered separately on Lead II. In recording the bipolar lead, a method similar to that described by Harris[5] was used. The electrodes were made of No. 18 cables. From each cable one of the thin wires constituting the cable was separated, and after their enamel cover was removed, the wires were placed between the epicardium and the muscle by means of an ordinary needle or some similar method. This assured fixation of the wires for the duration of the experiment. It is a difficult procedure and has to be done very carefully in order to avoid injury to the underlying muscle. Any one of the electrodes employed for the bipolar lead was used as the exploring electrode for the unipolar lead. In this way, the explored region was the same for both leads. The electrodes of the bipolar lead were connected with the cables of Lead I without any special arrangement as any electrode works well with any cable. This is so, because, as will be seen later, the tracing registered with the bipolar lead shows a much greater deflection than the accompanying deflections, and it does not matter whether they be positive (Fig. 7) or negative (Fig. 8).

Morphology of the Tracings Obtained by Closely Adjoining Electrodes.—If the electrodes are close enough to each other, a single rapid deflection is inscribed (Fig. 9) of shorter duration than the QRS complex in the standard leads. It may be a positive or a negative deflection, depending upon how the connection was made and upon which of the electrodes in contact with the muscle is activated first. More often there are one or two deflections besides the main one (Figs. 5 and 6). These may precede or follow the latter, and are of considerably less amplitude.

Theoretically, it may be accepted that the deflection of greatest amplitude is due to the activation of the muscular portion underlying the two electrodes and for this reason is an intrinsic phenomenon. The solid angle comprising more or less distant portions is almost the same for both electrodes, since they are very close to each other. It is evident that if the electrodes are fixed on the anterior aspect of the right ventricle the activating forces produced in the interventricular septum and in the free wall of the left ventricle influence both electrodes equally, and for this reason they are not manifested graphically. The smaller deflections are extrinsic phenomena as will be brought out later.

Harris[5] uses the term "pre R" wave to designate one of the smaller deflections when it happens to precede the greater deflection, and, concerning its meaning, he states that "the pre R deflections are probably not due to action currents

from subendocardial conducting tissues, but they are associated with the conduction that takes place under the external surface of the ventricle."

Facts in Favor of the Statement That the Main Deflection of the Bipolar Lead is the Manifestation of an Intrinsic Phenomenon.—

1. *Experimental right bundle branch block*: The electrodes were placed close to each other on the anterior aspect of the right ventricle (Fig. 1,*A*) and after registering the control, the right branch of the bundle of His was tapped

Fig. 1.—Experimental production of right bundle branch block. *A*, control tracing—bipolar lead. *B*, bipolar lead after production of block. The complexes in the bipolar lead are the same before and after the production of block. *D2* corresponds to Lead II.

with a steel rod in order to produce right bundle branch block (Fig. 1,*B*). The curve obtained before and after the block is the same in spite of the fact that septal activation has been greatly modified and the activation of the free wall of the right ventricle is delayed. We assume, therefore, that our bipolar curve is not influenced by the activations of the septum and the left ventricle. In other words, the concepts expressed concerning the solid angle are correct. Lead II changed considerably with the block and is very characteristic of it. The bipolar tracing did not change in morphology, but it was inscribed 0.04 second later in the ventricular complex (compare its relations with Lead II), since the activation of the septum now takes place from left to right.

2. *Experimental production of right and left ventricular extrasystoles*: It is well known that in left ventricular extrasystoles the activation first takes place in the left ventricle, next in the septum, and finally in the right ventricle. In right ventricular extrasystoles the process starts in the right ventricle, continues in the septum, and ends in the left ventricle. The general direction of the excitation wave is quite different in the two types of premature beats. The bipolar leads are not modified during the production of extrasystoles (Fig. 2),

and if they do suffer a change, it does not take place in the main deflection but in the smaller ones. This means that the largest deflection is intrinsic in nature and that it is produced by the action current of the muscle fibers close to the electrodes. The smaller deflections are extrinsic phenomena, probably due to activa-

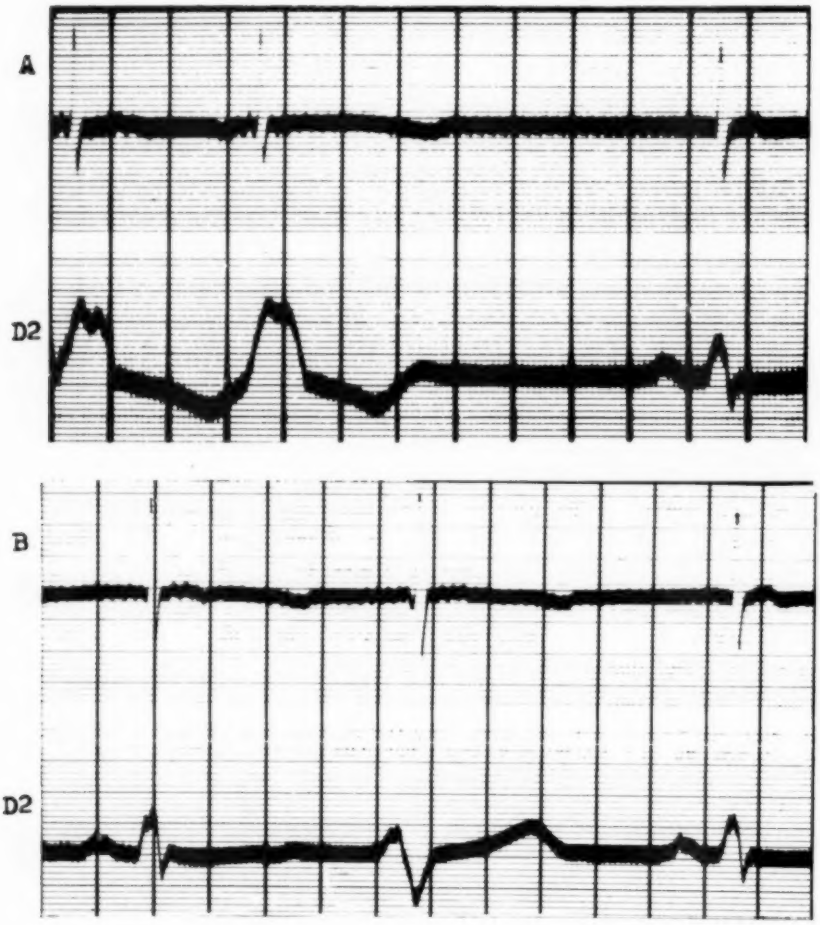

Fig. 2.—Experimental production of right and left ventricular extrasystoles. The first two complexes in *A* correspond to right ventricular premature beats, and are therefore positive in Lead II. The second complex in *B* is a left ventricular extrasystole and is therefore negative in Lead II. In the bipolar lead (*A* and *B*) the sinus complexes are practically the same. *D2* corresponds to Lead II.

tion of fibers not too far from the electrodes. This coincides with Harris' conception.

3. *Production of injured tissue at the site of the electrodes*: After the control tracing was inscribed, a few drops of potassium chloride were applied over the electrodes. The main deflection practically disappeared (Fig. 3) and two small deflections remained. When the subepicardial muscular tissue is injured, the action current of the fibers in contact with the electrodes disappears, the intrinsic

potential is eliminated, and the main deflection disappears or is depressed (Fig. 4).

Working with a bipolar lead consisting of closely adjoining electrodes in a heart in situ, surrounded by conducting tissues, is very similar to working with isolated muscular tissue not submerged in a large volume conductor. The main

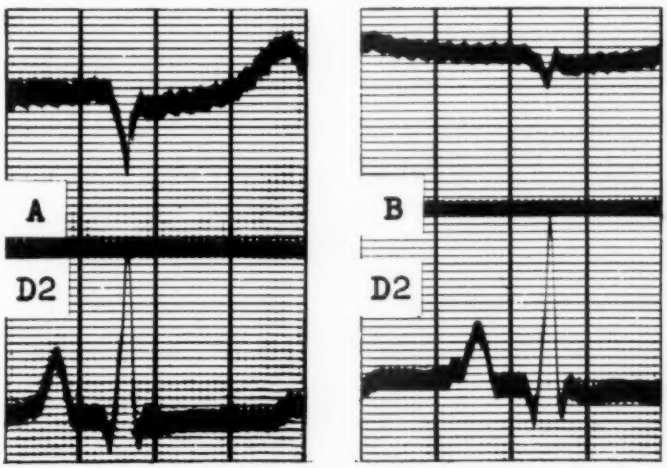

Fig. 3

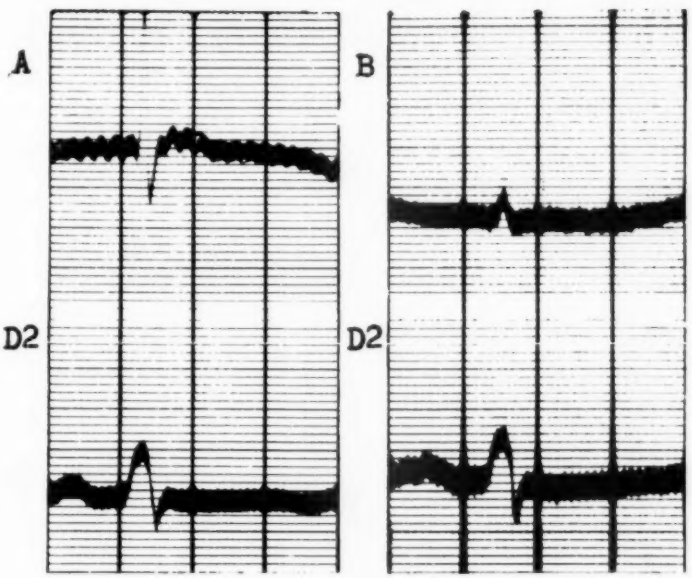

Fig. 4

Fig. 3 and Fig. 4.—Changes produced in the bipolar lead by injured tissue. *A*, control tracing with contiguous electrodes. *B*, after injury to the muscle in contact with the electrodes was produced. *D2* corresponds to Lead II.

similarity consists in the fact that the potential variations produced at a distance from the electrodes do not appreciably affect the tracing. Only changes in the muscle directly in contact with the electrodes are registered. In an isolated muscle fiber, the tracing which records cellular depolarization consists of a single deflection very similar to the one we have obtained with the bipolar lead. It is obvious why there are no secondary deflections; the phenomenon is simpler and there are no extrinsic variations. If half of the muscular fiber is activated and the other half is not, at this particular moment the apex of the deflection is inscribed. This is so because the activated part is relatively negative to the

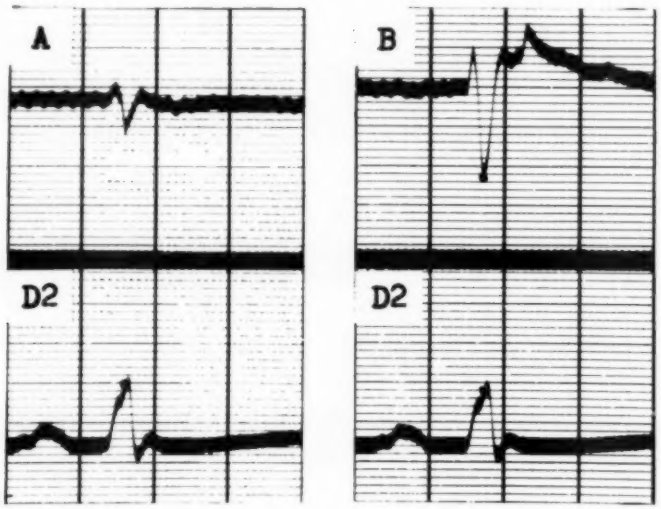

Fig. 5.—Tracings obtained from the trabecular zone of the right ventricle. *A*, bipolar tracing with contiguous electrodes. *B*, unipolar tracing. The points marked by dots correspond to the moment in which the wave of excitation reaches the subepicardial muscle. *D2* corresponds to Lead II.

part not activated. The small portion of muscle in contact with both electrodes of the adjoining bipolar leads may be considered as an isolated muscle fiber. When half of this hypothetical isolated muscle fiber is activated, or, in other words, when the muscular fibers in contact with one of the electrodes have been activated, at that moment the apex of the greatest deflection is inscribed. We can infer also that at that same moment the activation wave reaches the epicardium.

In the preceding discussion it is seen that the arrival of the excitation wave is recognized through its effect on a group of fibers. The activation of a portion of muscle is a process that requires a certain length of time and the negativity which it determines increases up to a certain limit. We have chosen the moment when the process is at the middle of our hypothetical isolated muscular fiber. Harris has chosen the beginning of the process which coincides with the beginning of the greatest deflection of the bipolar curve. The point chosen by us corresponds, according to the experiments of Cole and Curtis,[6] to the abrupt decrease in the impedance of the cell membrance.

Determination in the Intrinsic Deflection of the Arrival of the Excitation Wave to the Subepicardial Muscle.—The apex of the greatest deflection of the bipolar

curve was referred to Lead II and then, the point thus marked in Lead II was transferred to the unipolar curve. In the unipolar lead this point always coincided with the intrinsic deflection and never with the extrinsic. In more than one-half of the tracings studied it corresponded with the lowest part of the intrinsic deflection; this lowest point is inscribed at the moment at which the excitation wave reaches the subepicardial muscle (Figs. 5 and 6) and this agrees

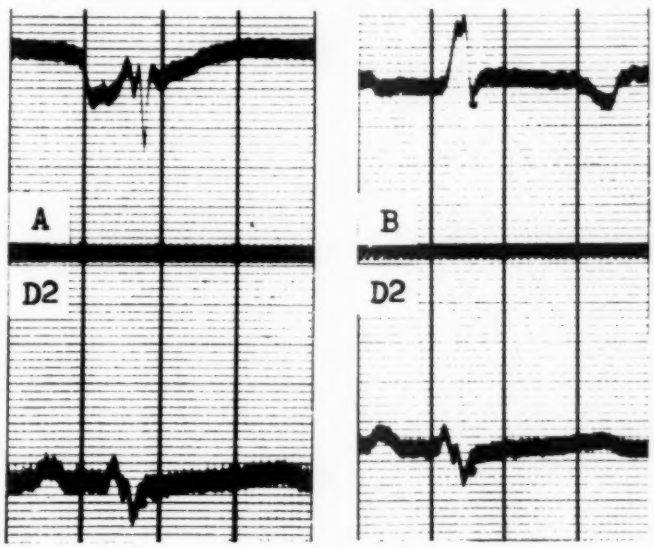

Fig. 6

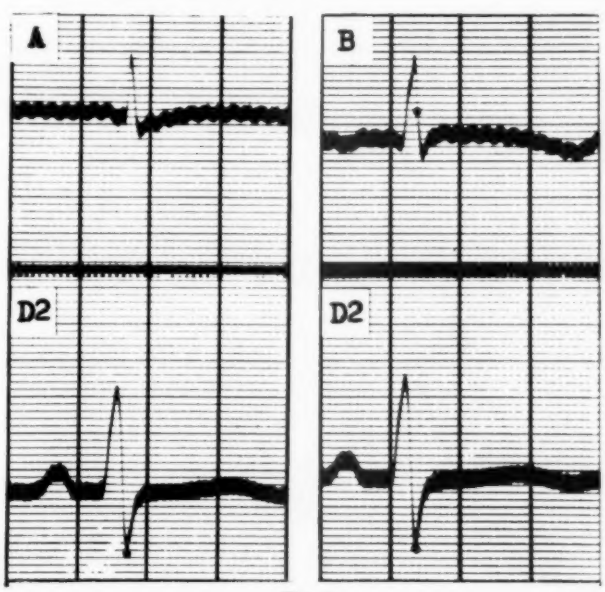

Fig. 7

Fig. 6 and Fig. 7.—Tracings obtained near the pulmonary conus. *A*, bipolar tracing with contiguous electrodes. *B*, unipolar tracing. The points marked by dots correspond to the moment in which the wave of excitation reaches the subepicardial muscle. *D2* corresponds to Lead II.

with the criterion recently set up by Wilson and associates.[4] Yet there are a number of tracings in which the point thus transferred to the unipolar curve did not occur at the lower apex of the intrinsic deflection but at some point on its lower third (Fig. 8) or lower half (Fig. 7).

In Fig. 5, the unipolar curve obtained at the trabecular zone of the right ventricle is of the rS type and the activation of the subepicardial muscle corresponds exactly to the lower apex of the intrinsic deflection. It coincides in Lead II with the ascending branch of the R wave at a point close to the apex.

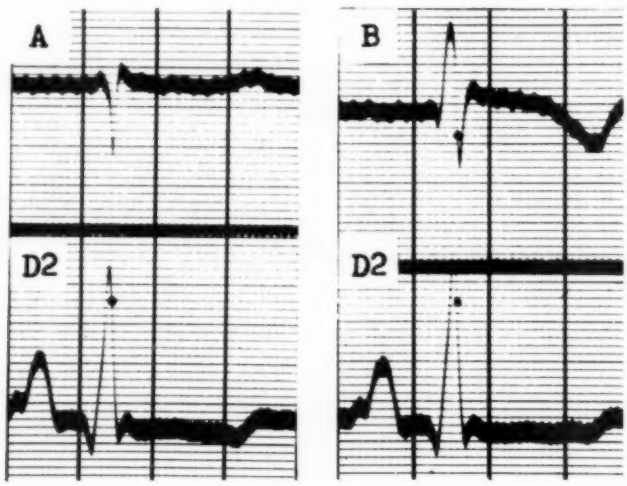

Fig. 8.—Tracings obtained near the apex of the left ventricle. *A*, bipolar lead with contiguous electrodes. *B*, unipolar tracing. The points marked by dots correspond to the moment at which the wave of excitation reaches the subepicardial muscle. *D2* corresponds to Lead II.

In Figs. 6 and 7 the unipolar curves, which were registered near the pulmonary conus, are of the Rs type, and the subepicardial activation which is quite delayed, does not occur at the same points in the intrinsic deflection. In one case it is at the bottom of the deflection and in the other it is near the middle of the deflection. In Lead II it is seen that the point is greatly delayed in the ventricular complex. This agrees with the well-known fact that the regions near the conus are the last to be activated.

In Fig. 8 the unipolar curve was registered near the apex of the left ventricle and the point which represents the activation of the subepicardial muscle is near the lower part of the deflection.

Some examples have been shown of the curves obtained, but it is convenient to point out that the experiments were numerous and similar results were always obtained.

By pressing slightly on one of the electrodes of the bipolar lead and using the same electrode for the unipolar lead afterwards, more or less pronounced shifts of the RS-T segment were obtained (Figs. 9 and 10), with a considerable diminution of the length of the intrinsic deflection in one case (Fig. 10). When the subepicardial muscle is injured by means of pressure, the excitation wave is

delayed. Nevertheless, its arrival corresponds to similar points previously described in the intrinsic deflection.

DISCUSSION

We have mentioned that Wilson[4] recently suggested that in precordial and unipolar leads the arrival of the stimulus to the subepicardial muscle corresponds to the lowest point of the intrinsic deflection. One explanation for this statement may be as follows. When a portion of the subepicardial muscle, let us say

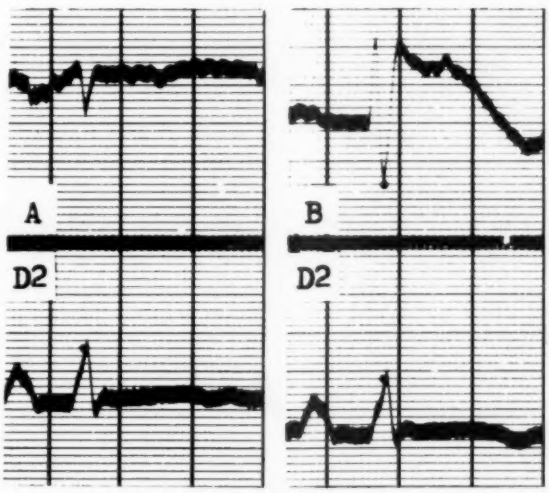

Fig. 9

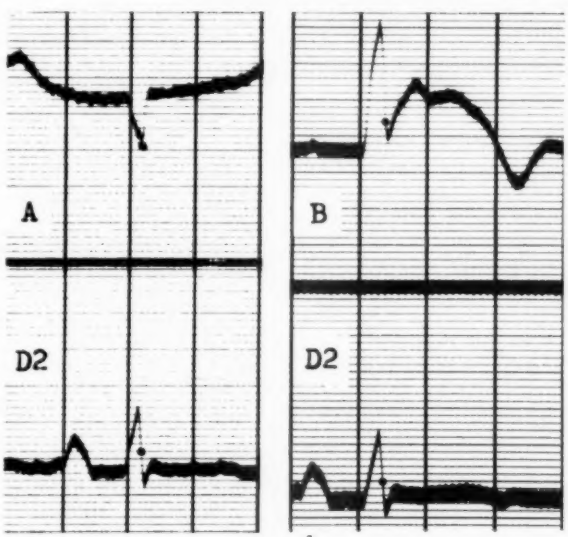

Fig. 10

Fig. 9 and Fig. 10.—Tracings obtained from the anterior surface of the right ventricle after injury of the fibers in contact with a single electrode. *A*, bipolar tracing with contiguous electrodes. *B*, unipolar tracing. The points marked by dots correspond to the moment at which the wave of excitation reaches the subepicardial muscle. *D2* corresponds to Lead II.

at the apex, is activated, this point is converted into a sink of current for all those inactivated areas and therefore is strongly negative relatively. The other areas will be gradually activated and will cease to be sources of current with respect to the subepicardial muscle at the apical region. Thus the negativity of this zone will gradually decrease. This is equivalent to the statement that the excitation is produced at the lowest portion of the intrinsic deflection.

Another fact to be considered is that when the entire free wall underlying the electrode is activated, it operates as conductive tissue and transmits the greater negativity of the intracavity potential. If this negativity is great enough to maintain or to increase the negativity of the exploring electrode, even after the underlying muscle is activated, it is evident that the lowest point of the deflection occurs later than the point which corresponds to the actual activation which is what we wish to determine. This explains those tracings in which the point representing the activation of the subepicardial muscle is above the apex of the intrinsic deflection.

We do not believe it to be fundamentally important in ordinary work to decide upon the exact point of the intrinsic deflection at which subepicardial activation occurs, but, from the academic standpoint, the concepts which have been discussed are important in order to have a clear idea of normal and pathological activation of the heart.

SUMMARY

1. The morphology and significance of the curves obtained by the method of adjoining bipolar leads, as described by Harris,[5] is studied.

2. It is proved experimentally that the greatest deflection of bipolar leads corresponds to the activation of the small muscular region in contact with the electrodes; indeed, it does not change in shape if right bundle branch block is produced or if premature contractions of right or left ventricle occur. On the contrary, the greatest deflection disappears or is reduced if the subepicardial muscular tissue in contact with the electrode is injured.

3. Reasons are given why the apex of the greatest deflection of the bipolar lead is chosen as the moment corresponding to the arrival of the activation wave at the subepicardial muscle.

4. Through the use of a simultaneously recorded Lead II the apex of the major deflection of the bipolar curve is referred to the intrinsic deflection of a unipolar curve. It is found that the lowest part of the intrinsic deflection or its lower third corresponds with the arrival of the wave to the subepicardial muscle.

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THE RESIDUAL BLOOD OF THE HEART

A Clinical X-ray and Pathologico-anatomical Study

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BY THE residual blood of the heart we mean the volume of blood which remains in the cavities after systole. Only Roy and Adami[1] and Starling,[2] have as yet discussed the question of whether residual blood is present under normal conditions.

The English clergyman, Stephen Hales,[3] in the eighteenth century was probably the first person to investigate the capacity of the heart chambers. He measured the capacity of the heart of a horse by filling it with melted beeswax and then calculating the displacement of the solidified mass. Similar experiments on hearts from cadavers were later made by Hiffelsheim and Robin[4] and by Hochrein.[5] Their experiments to estimate the capacity of the heart cavities are unique.

More than fifteen years ago Nylin[6] took special interest in the amount of residual blood under normal and pathological conditions and has been investigating the problem ever since in different ways and by different methods. He early called attention to the discrepancy between the volume of the heart at post-mortem examination (comprehensively investigated by Beneke,[7] Müller,[8] and Henle,[9]) and the teleroentgenological volume of the heart during life according to the Rohrer-Kahlstorf formula[10,11,12] which was confirmed by Lysholm, Nylin, and Quarnå[13] and later by Liljestrand, Lysholm, Nylin, and Zachrisson[14] and by Jonsell.[15] About the year 1880 the German anatomist, Beneke, calculated from cadavers the volume of the empty normal heart in adults to be 300 to 350 c.c., while Rohrer and Kahlstorf and the Swedish authors named found by x-ray examination that the heart volume of normal adults during life is about 700 cubic centimeters. This discrepancy may be explained by the fact that the heart in rigor mortis loses a part of its residual blood; it is not due to errors in method. Nylin[16,17] has pointed out several times that in clinical cases also this discrepancy between the volume during life and after death is most pronounced in cases of cardiac insufficiency with cardiac dilatation. Detailed investigations of the relation between the amount of residual blood and the circulation time have been carried out by Nylin and his co-workers.[18-21]

In this connection I should like to discuss the Rohrer-Kahlstorf formula for the determination of heart volume. This calculation is made with the help of sagittal and frontal orthodiagrams, and is based upon the assumption that the

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heart is between a paraboloid and an ellipsoid in shape. The formula has been modified for teleroentgenographic study by Liljestrand, Lysholm, Nylin, and Zachrisson,[14] and later by Jonsell,[15] and in Sweden this modification is generally employed for the determination of heart volume.

Kahlstorf has performed some experiments to compare the volume of hearts removed from cadavers, as calculated by orthodiagram, with the volume as determined by the displacement method (Archimedes' principle). The difference between the orthodiagraphic volume and that obtained by displacement did not exceed ± 5 per cent.

It is almost certain that changes in the amount of the residual blood are very closely related to the degree of dilatation of the heart. In general, dilatation occurs as a result of the following factors (Moritz)[22]: (1) a mechanical defect in the valves (stenosis or insufficiency, or a combination of both), (2) a primarily weakened myocardium, and (3) an increased peripheral resistance.

In these different conditions a certain volume of blood is retained after every systolic contraction. This volume of inactive blood causes the heart to start the next systolic contraction in a state of preliminary tension, which means that there is added pressure. This automatic utilization of the reserve forces is an application of "the law of the heart" (Starling).[2]

Our investigation is divided into two parts. The first part consists of calculation of residual blood during life in six patients having decompensated rheumatic valvular disease with considerable enlargement of the heart. The second part consists of a comparison of the volume of the heart, as determined by post-mortem teleroentgenography, and the volume of the heart, which had been removed from the body with all the vessels ligated, as estimated by the displacement method. This section is composed partly of studies of the six patients with rheumatic disease and partly of studies of four patients with a normal heart volume. The investigation was an attempt to prove the reliability of the teleroentgenological method of determining heart volume in adults. All the patients were treated in the South Hospital (Södersjukhuset), Stockholm. The investigations were performed in cooperation with the chief cardiologist, Professor G. Nylin, the chief radiologist, G. Jönsson, M.D., and the chief pathologist, F. Wahlgren, M.D.

METHOD

A post-mortem determination of the heart volume was made by x-ray, using the same focal distance (1.5 meters), as is used in determinations during life. A special roentgen table was required. In order to mark the posterior border of the heart, a special rubber tube was inserted into the esophagus since without an exact posterior delimitation the sagittal diameter of the heart shadow cannot be measured, nor the volume determined. After the x-ray examination, the heart was immediately removed, with all vessels carefully ligated.

The volume of the pericardial fluid was also measured. This procedure requires much time and has to be carried out with great care, as damage to any cavity of the heart or even very slight mechanical pressure on the organ might cause a loss of residual blood. In cases of extreme dilatation the auricles were

punctured and calculations of the aspirated volume of residual blood were made before removal of the organ. Then the heart was immersed in a large cylindrical vessel filled with water, the displaced water being collected in a graduated beaker. Thus the quantity of water displaced corresponded almost exactly to the heart volume. The organ having been weighed, the cavities were emptied and the residual blood was calculated directly in cubic centimeters. Finally the volume and weight of the "empty" heart muscle was calculated.

Fig. 1.—*A*, the heart volume during life was found to be 3,400 c.c. *B*, the heart volume after death was found to be 2,200 c.c.

RESULTS

These investigations have shown that during life the hearts of decompensated patients contain considerable quantities of residual blood. We are able to obtain an idea of the volume of residual blood *during life* through calculating by x-ray studies the difference between the total volume of the heart during life and the volume after death, the difference corresponding to the volume of residual blood expelled in rigor mortis (Figs. 1 to 4), and by adding to this difference the volume of residual blood present post mortem (measured directly by evacuation of the heart chambers). This method was first pointed out by Nylin. We have been able to show that over 50 per cent of the total volume of the heart during

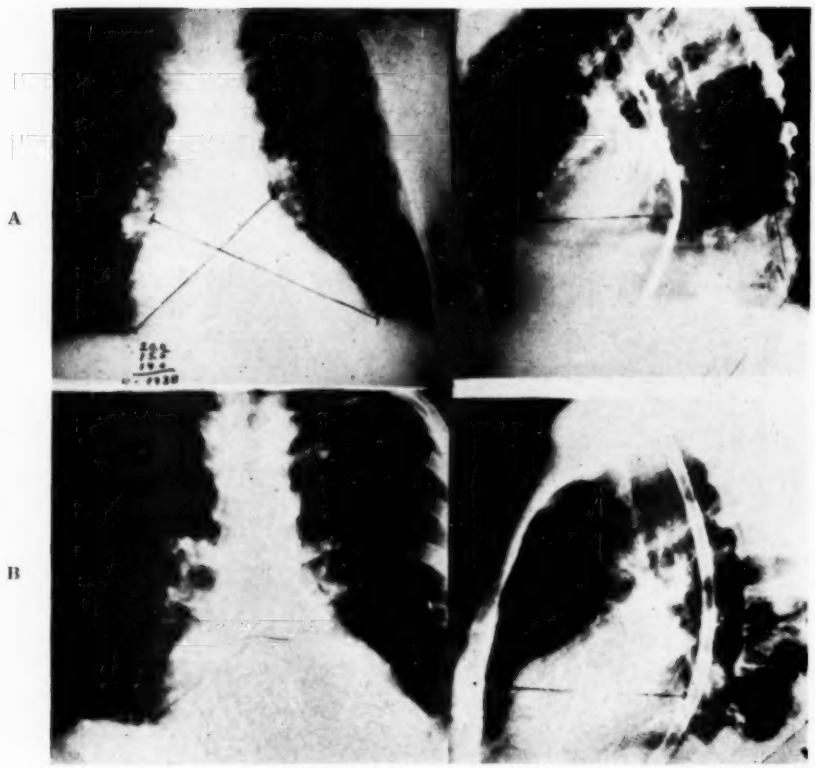

Fig. 2.—*A*, the heart volume during life was found to be 1,830 c.c. *B*, the heart volume after death was found to be 1,540 c.c.

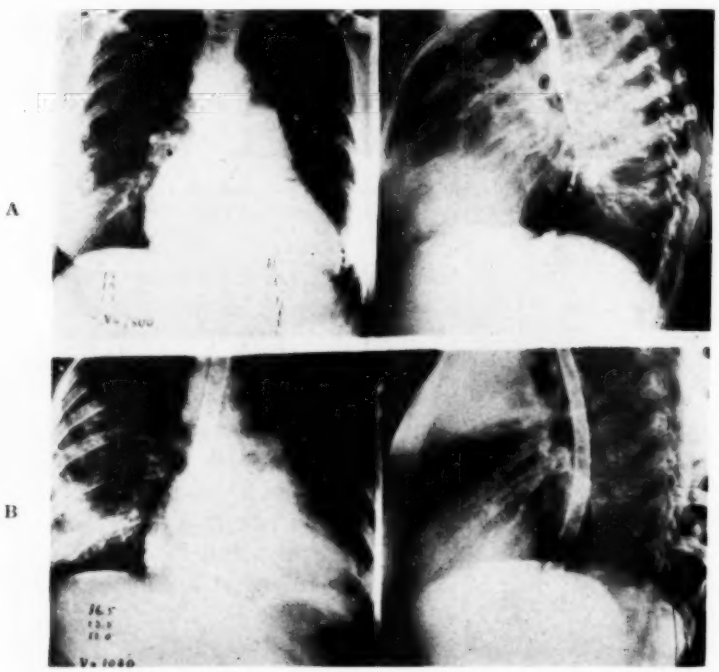

Fig. 3.—*A*, the heart volume during life was found to be 1,800 c.c. *B*, the heart volume after death was calculated to be 1,020 c.c.

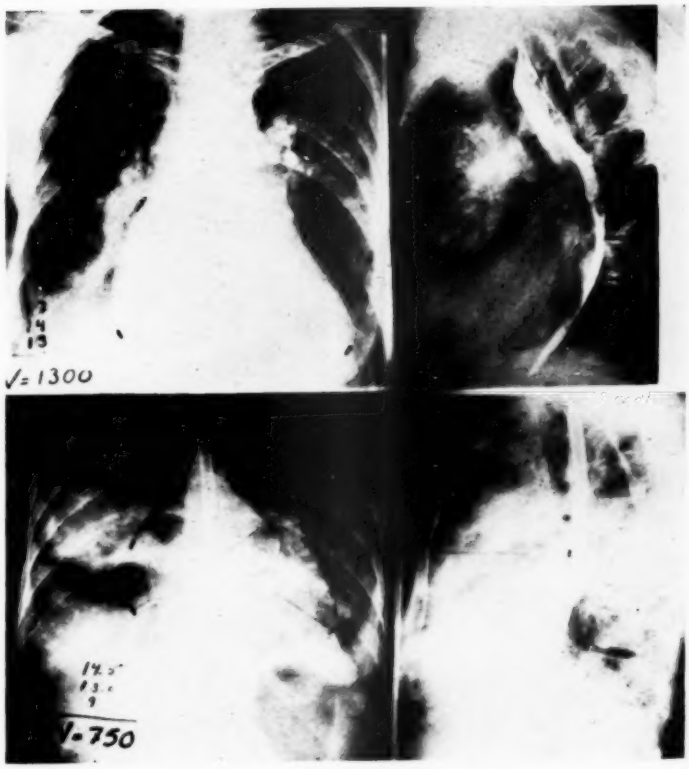

Fig. 4

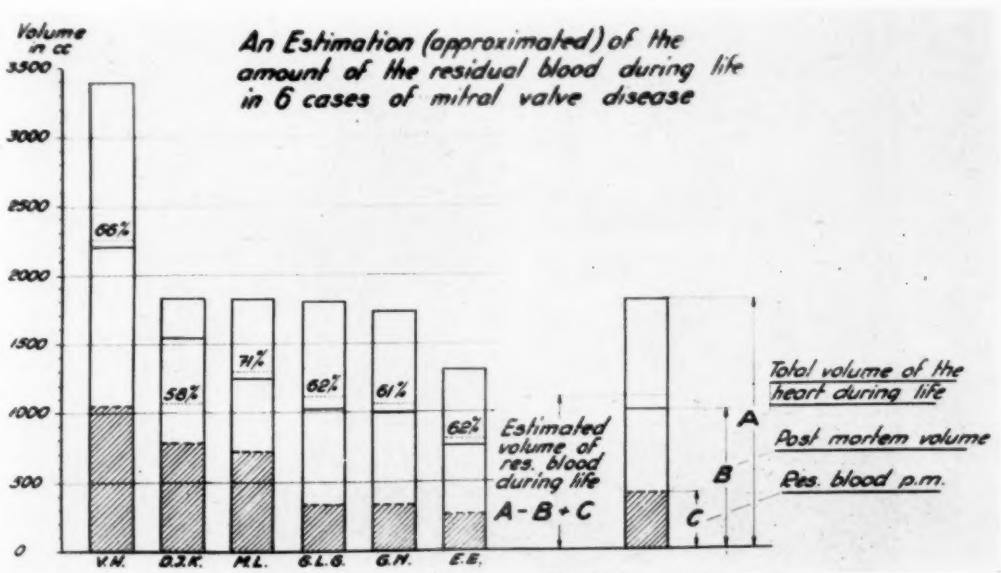

Fig. 5

Fig. 4.—*A*, the heart volume during life was calculated to be 1,300 c.c. *B*, the heart volume after death was calculated to be 750 c.c.

Fig. 5.—The difference of the heart volume before and after death plus the residual blood post mortem states an approximation of the amount of the residual blood during life.

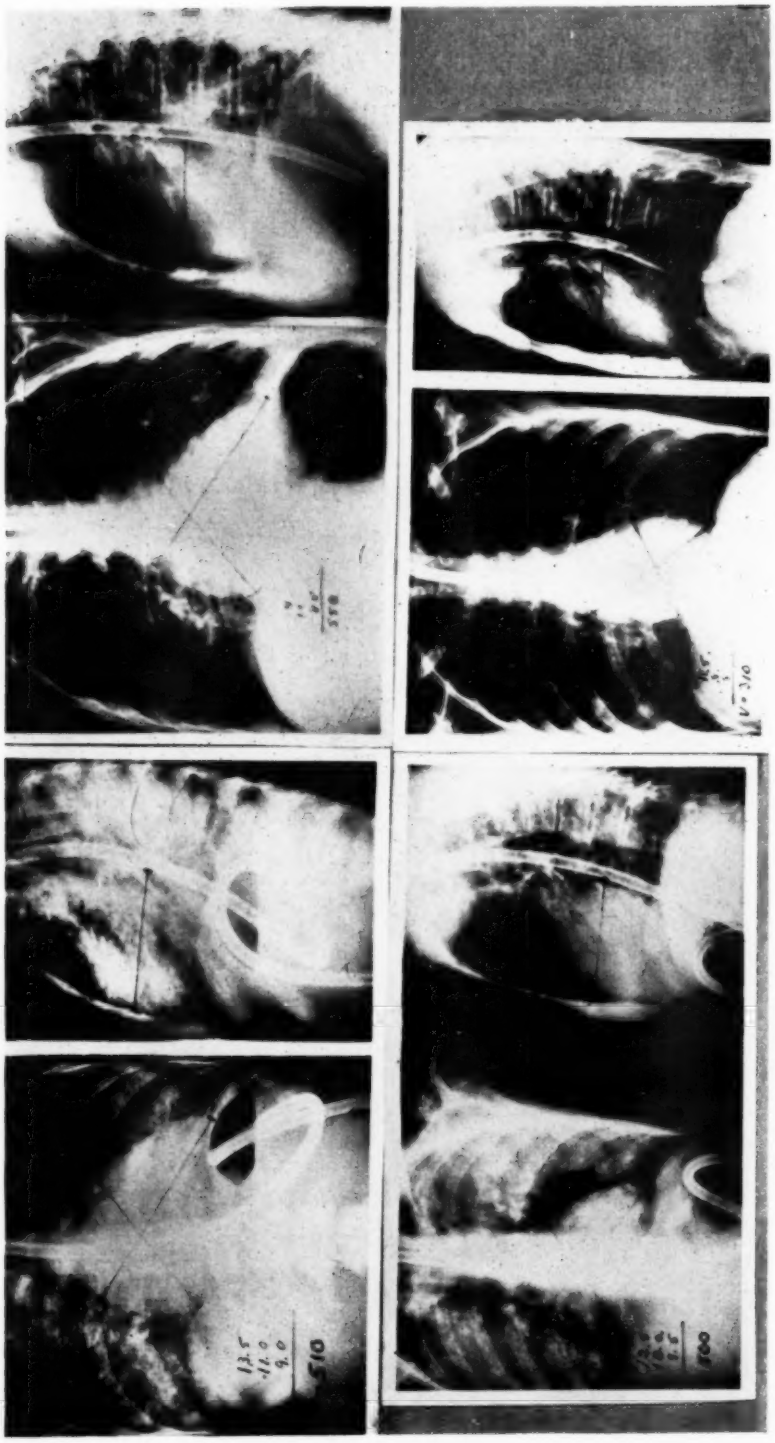

Fig. 6.—Four subjects, not suffering from heart disease, with normal heart volumes post mortem.

life consists of residual blood. The values lie between 58 per cent and 71 per cent of the total heart volume during life (Fig. 5). The heart volume has naturally not been the same for each individual case in the different x-ray determinations made. The calculations have been made in reference to the last ante-mortem volumes, which, in these cases, were obtained one to three weeks before death. The volumes of residual blood during life may be regarded as minimum values, as we have reason to assume that just before death the heart dilates extremely and the volume increases.

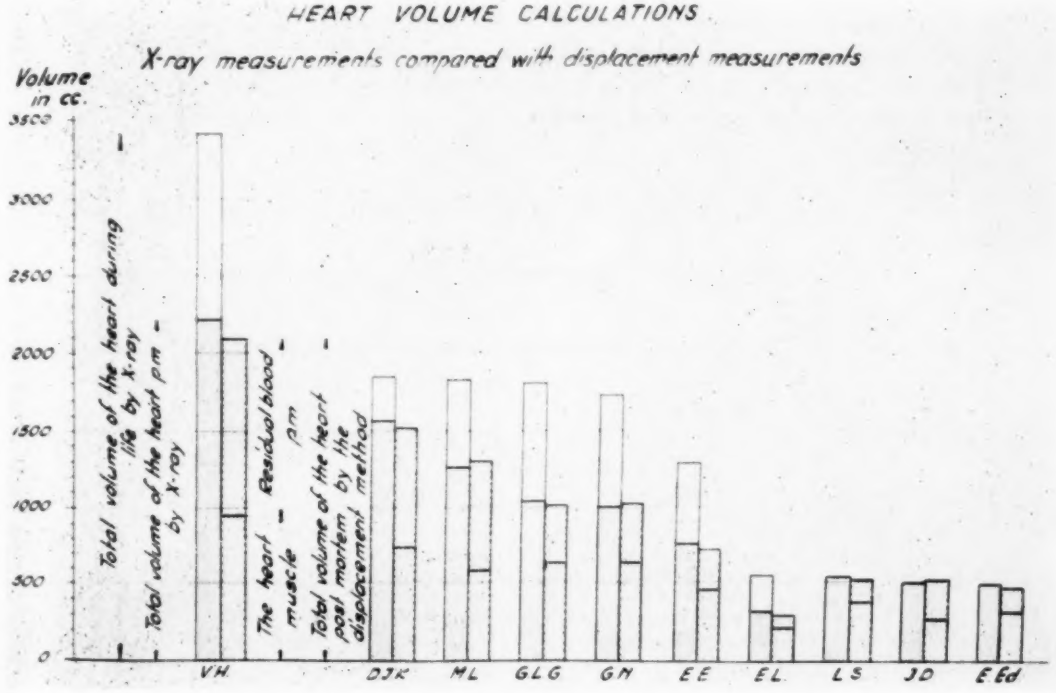

Fig. 7.—Six patients with valvular disease with considerable enlargement of the heart and four subjects with a normal heart volume. There is good agreement between the heart volume found by x-ray determination post mortem and the volume found by the displacement method.

This investigation also has shown the accuracy of the x-ray method for determining heart volume. Judging from this small amount of material, the Rohrer-Kahlstorf formula, modified by Liljestrand, Lysholm, Nylin, and Zachrisson[14] and Jonsell,[15] seems to express the real size of the heart, as there is particularly good correlation between the displacement of the removed organ, including the volume of the pericardial fluid, and the roentgenological heart volume present post mortem (Fig. 6). The determination by the displacement method does not deviate more than 5 per cent from the determination by the x-ray method (Fig. 7).

COMMENTS AND CONCLUSIONS

This investigation has shown the obvious decrease in heart volume with rigor mortis. Other factors too, such as the expiratory position after death and

certain static changes, might contribute to the decrease in volume. The discrepancy between the volume before and after death is of great interest for the pathologist as well as physiologists and clinicians. In one of the cases the heart had decreased in volume by about 50 per cent.

The knowledge that large amounts of residual blood are present during life in decompensated valvular heart disease accords very well with the prolonged circulation time pointed out by Nylin[17] and later by Malmström and Nylin[18] and Gernandt and Nylin.[19]

The difference between the total volume of the heart during life and the volume of the heart muscle per se, which difference corresponds approximately to the volume of residual blood, emphasizes the meaning of the clinical term "dilatation." Added to the volume of residual blood is the relatively small stroke volume in cases of decompensation.

Under certain circumstances the heart, like the liver and the spleen, seems to function as a blood depot.

As yet it is too early to offer an opinion of the amount of residual blood in normal persons.

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INCIDENCE OF CARDIAC ENLARGEMENT IN NONDISABLING RHEUMATIC VALVULITIS

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THE occurrence of general cardiac enlargement, or single-chamber dilatation, in rheumatic heart disease patients with impaired cardiac function has been extensively studied and repeatedly shown to be extremely high. On the other hand, there have been very few studies of reasonably large groups of rheumatic cardiac subjects in whom no clinical evidence of impaired heart efficiency could be demonstrated. A review of the literature revealed no detailed analysis of the frequency of abnormal heart size or shape in individuals with mild, inactive, asymptomatic rheumatic heart disease. The results of a roentgenographic study of cardiac size and configuration in a group of young soldiers with completely asymptomatic rheumatic valvulitis are therefore presented.

MATERIAL AND METHOD

Approximately 47,000 soldiers, aged 17 to 34 years, at a large Basic Training Center were given careful, complete (U. S. Army 64) examinations by a specially designated examining unit to determine their physical and mental fitness for flying duties. During their stay at the Training Center the soldiers were conditioned by an arduous physical training program. All of the trainees had been examined for physical fitness at least once prior to their arrival at this station. Many had been examined several times.

The examining unit pertinent to this study consisted of Flight Surgeons, Aviation Medical Examiners, two experienced internists* whose primary interests were in cardiology, and the author as roentgenologist.

Each examinee filled in a specially prepared history sheet which called for specific answers concerning previous heart trouble, rheumatic fever, chorea, frequent upper respiratory disease, and allied conditions. The cardiac auscultations were performed by the Flight Surgeons or Aviation Medical Examiners in two rooms specially prepared to dampen extraneous sounds. Whenever a suspicious history was obtained, or murmur heard, the trainee was subjected to special study of his cardiac status. This included further investigation into the history, an estimate of the cardiac functional capacity, auscultation by the two cardiologists, electrocardiography, and a special four-film cardiac roentgenographic study with barium-opacified esophagus.[1]

*Major Robert K. Dixon and Captain John L. Hoffman.

CRITERIA OF ABNORMALITY

The basic, well-established characteristics of the various murmurs as to quality, volume, location, radiation, and distribution in the cardiac cycle were employed in establishing them as most probably organic. Almost always the two cardiologists concurred as to the nature of the murmur. In many subjects, a definite or highly suggestive history of a rheumatic fever manifestation during childhood gave additional confirmation concerning the organic status of the murmur.

As is well known, the determination of minimal cardiac enlargement roentgenographically is often extremely difficult, and occasionally may be impossible in the individual subject. However, when the statistical method is applied to a large number of subjects this difficulty is resolved to a considerable degree. Any significant number of values above the average range will, in great probability, represent actual cardiac enlargement in the large majority of these subjects. Therefore, the Ungerleider-Clark tables[2,3] were employed for the normal standards in the determination of enlargement of the cardiac transverse diameter. The comparative reliability of this method has been substantiated by several investigators[4,5] and by unpublished data of my own. About 90 per cent of Ungerleider and Clark's normal subjects and 95 per cent of 250 normal control subjects I have analysed showed measurements not exceeding 10 per cent greater than their predicted measurements for height and weight. The plus 15 per cent value included over 97 per cent of the normal control subjects of both series. In the present study measurements greater than 15 per cent above the predicted figure were considered as indicating enlargement of the transverse cardiac diameter. The only exceptions to this criterion were in a very small group of subjects with flat chests and depressed sterna. These persons frequently demonstrate a "flat" heart with a large frontal size and small depth.[6] In these examinees of the present study, qualitative estimations of enlargements were made.

The normal variation of the cardiac frontal area was found to be greater than that of the transverse diameter. For this index of heart size, measurements up to 25 per cent above the Ungerleider-Clark predicted area values were considered as within normal limits. Measurements greater than these were classified as demonstrating abnormal enlargement of the cardiac frontal area.

Left auricular enlargement was determined with the aid of a barium-opacified esophagus by a quantitative method which the author has found helpful in the diagnosis of minimal auricular dilatation.[1] The upper limit of normal was assumed to be that measurement which was not exceeded in 95 per cent of normal controls (i.e., the ninety-fifth percentile value). Gross enlargements of the left auricle were so qualitatively manifest by displacement of the esophageal shadow that quantitative measurements were unnecessary.

Enlargements of the left ventricle, right side of the heart, and pulmonary artery were noted from the abnormal appearance of the silhouette of these chambers. No satisfactory practical quantitative method for the determination of minimal enlargement of any of these chambers was known to the writer. Thus, the abnormalities noted were sufficiently great to be apparent qualitatively and therefore could no longer be classified as truly minimal.

RESULTS

Of the 47,000 examinees who received the 64 Flying Status examinations, 82 soldiers (0.17 per cent) with rheumatic valvulitis were discovered. All of the men had been examined at least once previously, and many had had several prior examinations. The 0.17 per cent incidence, therefore, is of no great significance since the data were obtained from a select population. A somewhat similar study, based on Army 64 examinations of about 45,000 air crew aspirants, revealed a 0.22 per cent incidence of rheumatic valvular disease.[7] These latter soldiers also had had at least one previous screening.

TABLE I. DISTRIBUTION OF VALVULAR INVOLVEMENT

MURMURS		NUMBER
Mitral insufficiency		53
Mitral stenosis		2
Aortic insufficiency		5
Combined forms		22
Mitral insufficiency and mitral stenosis	15	
Aortic insufficiency and aortic stenosis	3	
Mitral insufficiency and aortic insufficiency	1	
Mitral insufficiency and aortic stenosis	1	
Mitral insufficiency, mitral stenosis, and aortic insufficiency	1	
Mitral insufficiency, mitral stenosis, aortic insufficiency, and aortic stenosis	1	

None of the 82 examinees with rheumatic valvular disease gave any history of cardiac functional impairment, not even upon pointed questioning. The soldiers unhesitatingly admitted previous episodes of rheumatic fever attacks, but all insisted they were able to undergo the rigorous physical conditioning without any difficulties suggesting diminished cardiac capacity.

Table I shows the distribution of the valvular involvement among the 82 soldiers. Simple mitral insufficiency was observed most frequently. Combined lesions were observed more often than isolated mitral stenosis or aortic insufficiency.

The distribution of the valvular enlargement was correlated with the presence of a highly suggestive or definite history of previous rheumatic fever episode, in an attempt to determine any unintentional weighting of cases by a positive history. The results are shown in Table II. As is clearly evident, the distribution in the 28 men with a positive rheumatic fever history is essentially the same (subject to the usual statistical variations) as that in the larger group of 54 men with no positive history. Further, the incidence of a positive history appears no greater in those examinees with extensive anatomical involvement than in the soldiers with isolated deformity of a single valve.

The incidence of an abnormality of the cardiac silhouette is shown in Table III. Only 34 examinees of the 82 (41.5 per cent) with valvular disease showed any evidence of cardiac enlargement or silhouette abnormality. Of the 70 individuals in whom the pathological process was limited to the mitral valve, 27 (38.6 per cent) showed some deviation from the normal in the x-ray film of the heart.

TABLE II. INCIDENCE OF RHEUMATIC FEVER HISTORY AND TYPE OF VALVULAR INVOLVEMENT

MURMURS	RHEUMATIC FEVER HISTORY	NO RHEUMATIC FEVER HISTORY
Mitral insufficiency	18	35
Mitral stenosis	1	1
Aortic insufficiency	3	2
Multiple valvulitis	6	16
Totals	28	54

A significantly higher percentage of abnormal heart shadows occurred in patients with a double mitral murmur (8 out of 15 or 53.3 per cent) than in patients with isolated mitral insufficiency or stenosis (19 out of 55 or 34.5 per cent). All 4 subjects with combined mitral and aortic disease showed roentgenographic cardiac abnormalities.

TABLE III. INCIDENCE OF CARDIAC ROENTGENOGRAPHIC ABNORMALITY WITH VALVE INVOLVEMENT

VALVE			SOME CARDIAC X-RAY ABNORMALITY*		X-RAY FILM DEMONSTRATING NO ABNORMALITY	
Mitral		70	27		43	
Mitral insufficiency	53			19		34
Mitral stenosis	2			0		2
Mitral insufficiency and mitral stenosis	15			8		7
Aortic		8	3		5	
Aortic insufficiency	5			2		3
Aortic insufficiency and aortic stenosis	3			1		2
Combined mitral and aortic		4	4		0	
Mitral insufficiency and aortic insufficiency	1			1		0
Mitral insufficiency and aortic stenosis	1			1		0
Mitral insufficiency, mitral stenosis, and aortic insufficiency	1			1		0
Mitral insufficiency, mitral stenosis, aortic insufficiency and aortic stenosis	1			1		0
Totals		82	34		48	

*Enlarged transverse diameter, frontal area, or cardiac chamber. Does not include instances where accentuated pulmonary artery shadow is only abnormality.

In Table IV is shown the frequency of association of the various types of abnormalities of the cardiac silhouette with the different valvular involvements. Enlargement of the left auricle was observed most frequently, in 24 of the 82 subjects (29.3 per cent). In a number of men the enlargement was slight and could be demonstrated with reasonable certainty only by special technique.[1] In others, the auricular dilatation was sufficient to be quite apparent on routine fluoroscopy after opacifying the esophagus. The greatest incidence of a dilated left auricle was found in the subjects with double mitral lesions (7 out of 15,

46.6 per cent) and combined mitral and aortic involvement (2 out of 4). Of the 53 examinees showing isolated mitral insufficiency, left auricular enlargement was observed in 15 subjects, 28.3 per cent. Only 2 individuals with isolated mitral stenosis were observed. These showed no left auricular accentuation.

An enlarged cardiac transverse diameter was found in 13 examinees (15.8 per cent). The frontal area was greater than the designated normal limit in 18 subjects (22.0 per cent). Recognizable accentuation of the left ventricular contour was observed in 12 men. A cardiac silhouette suggestive of right ventricular enlargement was seen only twice, and the pulmonary artery segment of the heart contour was found accentuated in 7 subjects.

The number of examinees is too small for significant correlation between the type or location of the valvular lesion and cardiac enlargement. However, the findings do suggest that multiple valvular involvement or a double lesion on one valve is more likely to be associated with demonstrable cardiac silhouette abnormalities than single valve deformity associated with only one murmur.

TABLE IV. TYPE OF ABNORMALITY OF THE CARDIAC SILHOUETTE ASSOCIATED WITH VALVE INVOLVEMENT

MURMURS	NUMBER	ABNORMAL ROENTGENOLOGIC FINDINGS					
		ENLARGED TRANSVERSE DIAMETER	ENLARGED FRONTAL AREA	ENLARGED LEFT AURICLE	ENLARGED LEFT VENTRICLE	ENLARGED RIGHT VENTRICLE	ACCENTUATED PULMONARY ARTERY
Mitral insufficiency	53	6	9	15	4	2	6
Mitral stenosis	2	0	0	0	0	0	0
Mitral insufficiency and mitral stenosis	15	2	4	7	2	0	1
Aortic insufficiency	5	2	2	0	2	0	0
Aortic insufficiency and aortic stenosis	3	1	1	0	1	0	0
Combined mitral and aortic disease	4	2	2	2	3	0	0
Totals	82	13	18	24	12	2	7

DISCUSSION

The high incidence of cardiac enlargement in persons with rheumatic valvulitis has been constantly stressed and reiterated.[8-13] However, it is also moderately well recognized that patients with undoubted rheumatic valvular disease may show no cardiac enlargement whatever.[9,14-21] Many of the observers note that in the early stages the heart may be of normal size and shape, and only as the disease and functional aberration progress does cardiac enlargement appear. The possibility of extremely slow progression and long quiescence is well recognized by Sosman,[9] Parkinson,[24] Zdansky,[18] Roesler,[19] Palmer,[25] and Paterson.[21] During the phase of inactivity of the lesion and lack of cardiac embarrassment, the heart may appear entirely normal for long periods of time.

It thus becomes apparent that the incidence of cardiac enlargement is a directly varying function of the degree of rheumatic activity, myocardial damage, and amount of physiological impairment caused by the valvular deformity.

The frequency of roentgenographic cardiac abnormalities in rheumatic valvular patients with, or near, congestive failure appears to be nearly 100 per cent. Many of the authors referred to in the previous paragraphs concur in this opinion. Indeed, I believe it is to this class of patients that the New York Heart Association handbook makes reference when it states, "Enlargement of the heart may be slight and recognizable only on radiography, but without it deformity of the mitral valve should not be diagnosed."[12]

However, studies on the quantitative incidence of cardiac enlargement in persons with nondisabling rheumatic valvulitis have been almost nonexistant. De Balsac[20] estimates that about 10 per cent of the individuals with mitral disease show normal hearts radiographically. The only other statistical survey of subjects with functionally normal rheumatic valvular hearts found was that of Delaney, Miller, Kimbro, and Bishop.[7] These authors were also performing Army 64 examinations to determine fitness for military flying, and reported their findings in 100 U. S. Army World War II soldiers with completely compensated rheumatic valvulitis. They noted that an enlarged heart was present in only 28 per cent of the 100 men. Unfortunately, information as to their exact criteria of enlargement and chamber dilatation analysis in the various groups of valvular abnormalities was not presented. Nevertheless, because their data and the findings of this study represent the results of similar investigations of similar material, a comparison table (Table V) has been constructed to permit some combination of the material for increased statistical significance.

TABLE V. COMPARISON BETWEEN SURVEY OF FUNCTIONALLY NORMAL RHEUMATIC HEARTS OF DELANEY AND CO-WORKERS AND THAT OF PRESENT STUDY

MURMURS	DELANEY, MILLER, KIMBRO, AND BISHOP		AUTHOR'S SERIES	
	NUMBER	ENLARGED HEART	NUMBER	ENLARGED HEART
Mitral insufficiency alone	10	0	53	19
Mitral stenosis alone	4	0	2	0
Mitral insufficiency and stenosis	34	11	15	8
Aortic insufficiency alone	39	10	5	2
Aortic insufficiency and stenosis	4	3	3	1
Combined aortic and mitral disease	9	4	4	4
Totals	100	28	82	34

Several significant differences in the two groups may be observed. First, the incidence of isolated aortic valvular disease was far greater in the series of Delaney and co-workers (43 per cent) than in the present group (9.8 per cent). Indeed, their rate of aortic valvulitis is considerably higher than those reported

by other observers. The occurrence of isolated rheumatic aortic valve abnormalities in 3,760 cases in five large series [16,26-29] varied between 4.4 and 21.4 per cent, weighted average being 12.8 per cent. Secondly, while 19 of 53 examinees with mitral insufficiency showed cardiac enlargement of some type in this series (see Table IV) the other investigators reported none of their 10 subjects as showing a roentgenographic abnormality. At least part of this discrepancy in findings appears to be due to differences in criteria of enlargement. Delaney and associates apparently depended almost entirely on fluoroscopic study for the determination of left auricular enlargement. While this essentially subjective method is excellent in moderate left auricular dilatation, it may be too gross a method and quite inadequate for the determination of minimal left auricular enlargement.

There was general agreement of the two series in several major aspects. Essentially all the examinees of both groups showed no functional cardiac impairment of any kind. Double murmurs arising from a single valve and multiple valvular involvement were found associated with a considerably higher incidence of cardiac enlargement than were single murmurs either of the aortic or mitral cusps. The incidence of a cardiac silhouette abnormality was much lower than universally expected in the symptomatic rheumatic heart disease patients—28 per cent in one series and 41.5 per cent in the presented group.

The study indicates that the significance of cardiac enlargement in rheumatic heart disease must be re-evaluated in relation to the cardiac functional status of the patient. While individuals with overtly impaired cardiac function due to rheumatic carditis may be expected to show enlarged hearts in practically every instance, cardiac enlargement occurs in only 28 to 41.5 per cent of examinees not disabled by their rheumatic valvulitis. In some of these, the enlargement may be so minimal that its diagnosis may be doubtful. It is thus evident that roentgenographic methods are of distinctly limited value for the exclusion of the possibility of organic valvulitis in persons having cardiac murmurs but essentially normal functional capacity of the heart. On the other hand, when cardiac enlargement is found in such persons it is of definite aid in establishing the organic nature of the murmur.

CONCLUSIONS

1. During the careful physical examination of approximately 47,000 young soldiers to determine their fitness for flying, cardiac murmurs which were considered as being caused by organic rheumatic valvulitis were found in 82 examinees. None of these 82 men showed any evidence of impaired cardiac function.

2. A roentgenographic cardiac abnormality was observed in 34 (41.5 per cent) of these 82 examinees. Enlargement of the left auricle was observed in 24 (29.3 per cent).

3. Roentgen ray cardiac abnormalities were seen more frequently when multiple valves were involved or two murmurs on one valve heard than when a single murmur from a single valve was noted.

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THE DIGITAL BLOOD PRESSURE. I. VALUES IN NORMAL SUBJECTS

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A REVIEW of the literature reveals that there has been very little clinical investigation of the digital blood pressure. The opinion of some authorities[1,2] appears to be that digital pressures have such wide normal fluctuations that their measurement is of limited clinical value. Consequently, very little use has been made of this procedure which in our hands has proved to be simple and reliable. With a few minor modifications of previously used methods, we have found digital blood pressure measurements to be as consistent and almost as rapid as the routine brachial auscultatory method of blood pressure determination.

In 1899, Gaertner[3] described an apparatus (Gaertner's capsule) for the indirect measurement of digital blood pressure. The apparatus consisted of a metal ring lined on its inner circumference with a rubber membrane to form an airtight cuff having manometer connections. The subjects finger was blanched by rolling a rubber band down to the digit's base. The capsule was then placed around the base of the finger and the membrane inflated well above the expected systolic pressure. The rubber band was severed and the capsule slowly deflated until a flush appeared on the finger distal to the cuff. This point was the systolic pressure. As the cuff was further deflated the subject felt pulsations in the finger. The point at which the pulsations ceased was considered to be the diastolic pressure.[4] Employing Gaertner's technique, several observers have studied the digital arterial pressure and are in fair agreement regarding the normal slope of gradient between the brachial and digital arteries. In eight normal subjects, Cohn and Lundsgaard[5] found the average digital systolic pressure to be 20 mm.Hg lower than the auscultatory brachial systolic pressure, with a gradient range between 5 and 30 mm. of mercury. They employed the blanching technique but used a Von Recklinghausen type cuff instead of the Gaertner capsule. They found the digital method to be valuable in determining blood pressures in patients with auricular fibrillation when the brachial blood pressure was widely fluctuant. They considered the digital pressure to be more stable than the brachial under these circumstances, because in experimentally produced fibrillation in the dog the systolic pressure in the foot fluctuated through a smaller range than the systolic pressure at the thigh level.[6]

Using the Gaertner capsule, Hayashi[7] found the average normal brachial-to-digital pressure gradient to be 20 mm. of mercury. Average gradients were the same in men, women, and children.

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Doleschal[8] found the digital pressure taken with the Gaertner capsule always lower than the radial arterial pressure.

Oppenheimer and Prinzmetal,[9] using a modified Gaertner capsule, reported an average brachial-to-digital systolic gradient of 29 mm. Hg in 25 subjects with normal brachial blood pressures.

Mendlowitz[4,10] determined both systolic and diastolic digital pressures with the Gaertner capsule (diastolic subjectively determined by cessation of throbbing). Using calculation of systolic and diastolic arithmetic means, he presented figures which he felt indicated a diminution in brachial-to-digital pressure gradient in secondary clubbing of the fingers. The gradient range for his group of normal subjects was roughly similar to the results of Oppenheimer and Prinzmetal.[9]

Wishart[1] made blood pressure determinations on various portions of the extremities using an original and interesting type of oscillometer based on the principle of Whiddington's ultramicrometer.[11] Systolic and diastolic values are determined by the change in pitch transmitted from the apparatus through a loud speaker as the cuff pressure is lowered. By this method Wishart found brachial systolic readings about 4 mm. higher than by the usual auscultatory method. These higher values compare favorably with direct brachial systolic readings determined with the Hamilton manometer.[12,13,14] Wishart[1] found good agreement between his brachial diastolic readings and those determined by the auscultatory method when using the fourth phase of the Korotkoff sounds. He found digital blood pressures determined by this method satisfactory only when pulsations of good amplitude were present. In normal subjects the digital systolic and diastolic pressures were 20 to 30 mm. Hg lower than pressures at the wrist.

Formijne,[2] who used a modified Gaertner capsule as an oscillometer in the study of peripheral vascular disease, has pointed out the value of this principle in studying blood pressure in obliterative arterial disease since it is the best practical means for determining arterial blood pressure which is not dependent on arterial pulsations.

From reported figures then, it appears that in normal subjects the digital systolic blood pressure averages about 20 to 30 mm. Hg lower than the brachial systolic pressure, and the range in gradient lies roughly between 5 and 40 mm. of mercury. The diastolic brachial-to-digital pressure gradient seems to have a similar slope, although reported figures are too few for definite conclusion.

With the modified method we are describing it seemed desirable to measure digital pressures on a sufficiently large group of normal subjects to determine whether the brachial-to-digital gradient ranges within narrow enough boundaries to permit this measurement to be a useful clinical tool. After a few minor improvements it soon became evident that the method was reliable and that fluctuations in readings were sufficiently small to give results as consistent as those found on auscultatory brachial pressure readings. The brachial-to-digital pressure gradients in hyperthyroidism and certain other diseases were found to be well outside of the sharply defined limits of normal and will be reported in a subsequent paper.

MATERIAL AND METHODS

The cuff (Fig. 1) is similar in design to the ordinary commercial sphygmomanometer cuff consisting of a rubber bladder inside of a cloth cuff. The portion of the cuff containing the bladder (a condom makes an ideal bladder) is 4 cm. wide and 14 cm. in length. The tail of the cuff is about 20 cm. long and tapers off to an end of about 1 cm. in width. Two small, rubber catheter tubes are attached to the side of the bladder. Originally the connection between hose and bladder produced a nodular irregularity on the otherwise smooth cuff, and it was found that such a design gave inconstant results. In order to avoid these local areas of increased pressure against the finger, the connections were placed in two small out-pouches on the lateral wall of the cloth cuff. One rubber tube is connected with an ordinary mercury manometer and the other is attached to a bulb.

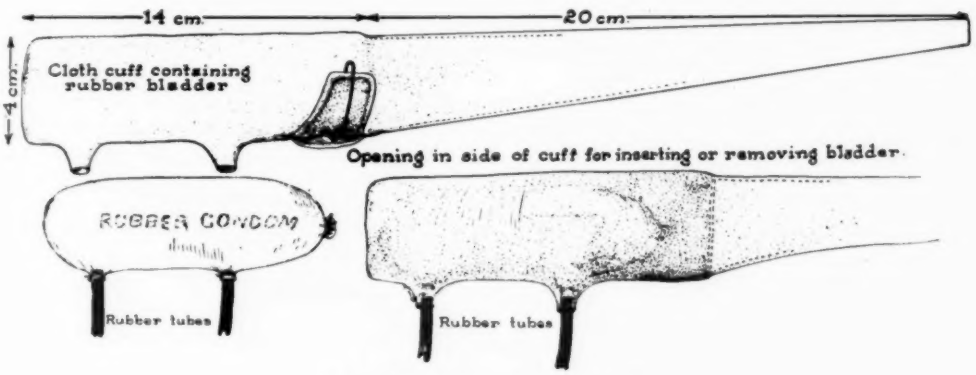

Fig. 1.—Digital blood pressure cuff.

The cuff may be used on any finger or on any toe that is of sufficient length to leave a liberal portion of the end of the digit exposed. A short toe requires a narrower cuff.

The cuff is wrapped snugly about the proximal phalanx of a digit (Fig. 2). Although looseness or tightness of wrapping appears to have no effect on readings within fairly broad limits, the cuff should not be so tight that it causes venous obstruction nor so loose that it slides on the digit. The end of the digit is then blanched by firmly wrapping it from tip to cuff border with a strip of rubber (dental rubber dam cut to about 4 by 16 cm. is adequate) (Fig. 3, *A* and *B*). The pressure in the cuff is raised to a level well above the expected systolic pressure. The rubber wrap is removed and cuff pressure slowly lowered until a flush appears in the blanched end of the digit (Fig. 3, *C* and *D*). The manometer reading at this point is the systolic pressure. If the cuff is deflated too rapidly, an error of several millimeters will be introduced since a small amount of time is required for the first jet of blood that passes through the digital artery to reach skin level. For uniform readings, when the manometer is 6 to 8 mm. above the expected systolic pressure, the cuff is deflated at about the speed required to read aloud slowly each even number that the mercury passes on the manometer scale.

More accurate results will be obtained if a second individual watches for the end point.

On lowering the cuff pressure, the end point is indicated by a distinct flush of the tip of the digit. Following the first faint flush the entire end of the digit becomes red within a further 2-mm. pressure lowering. Vasospasm peripheral

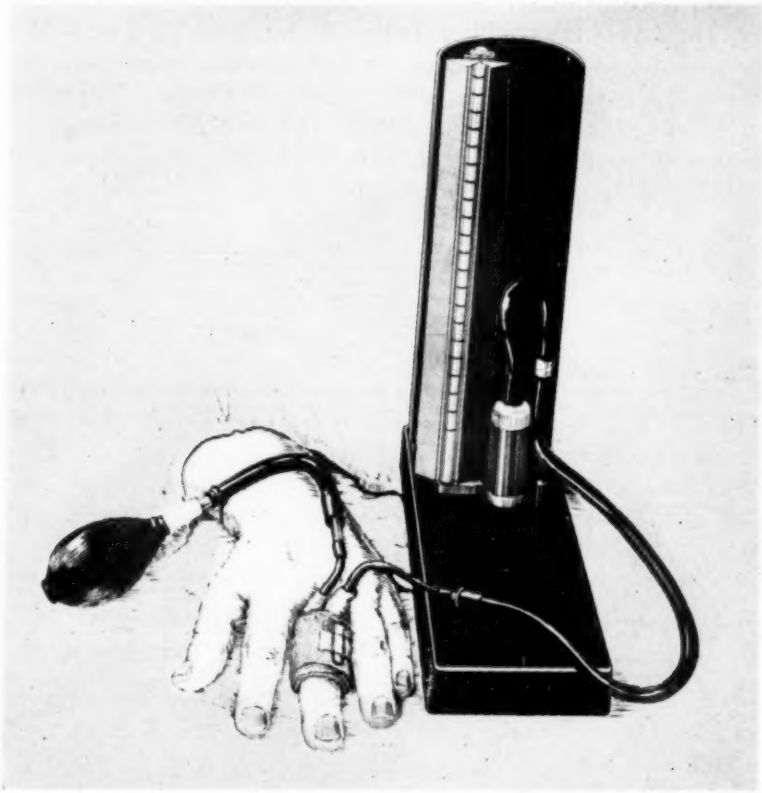

Fig. 2.—Digital cuff in place. Dorsal view shown to demonstrate connections with manometer; when determinations of digital pressure are made the hand is supinated.

to the digital artery might be expected to produce a gradual appearance of the flush in the blanched end of the digit, but since a rapid end point nearly always appears it seems that an extreme of vasospasm is necessary to alter significantly the sharpness of the end point.

There were occasional isolated readings in which the flushing appeared very slowly over a span of about 10-mm. deflation, thus producing an indefinite end point. There was no apparent relationship between these poor end points and sighing or sensory stimulations. The reading taken immediately afterward always showed the usual sharp end point at a similar pressure level as on earlier readings. This gradually appearing flush may have been caused by a wave of vasospasm,[15-18] occurring just at the chance moment when the falling pressure of the cuff was approaching the systolic level.

When the cuff pressure is near the systolic level the subject will often feel pulsations of his digital artery under the cuff. As the cuff is further deflated, the pressure at which pulsations suddenly cease is considered to be the diastolic pressure.

The position of the hand appears to have some influence on digital pressure. When the hand is turned so that it rests on its ulnar edge the flush often appears several millimeters lower than when the hand is lying flat with the palm upward. This was not a consistent finding but presents a possible source of error if disregarded.

Fig. 3.—Demonstration of the technique for the determination of digital blood pressure.

In the data to be presented, each blood pressure value represents the average of at least two readings. These nearly always checked within 4 millimeters. Digital pressure determinations were alternated with brachial auscultatory blood pressure readings and the entire series of observations was usually completed in eight minutes. All subjects were recumbent with the arm and finger at the level of the heart. The arm was placed comfortably so that it approximated a 30-degree angle with the body since it has been shown that the brachial systolic pressure is altered when the arm is parallel to the body.[19]

RESULTS

Digital systolic pressure (Table I).—The group consisted of seventy-five subjects (sixty male and fifteen female subjects) with normal brachial blood pressures. The ages ranged from 16 to 65 years with all but fifteen subjects below 50 years. Thirty-four were members of the house staff, technicians and other workers and the others were selected at random among hospital patients with no known cardiovascular disorder.

TABLE I. BLOOD PRESSURE VALUES IN NORMAL SUBJECTS

NAME	AGE	SEX	PULSE RATE	BRACHIAL		DIGITAL SYSTOLIC (MM. HG)	BRACHIAL DIGITAL GRADIENT (MM. HG)	DIAGNOSIS
				SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)			
Fu	60	M		122	71	117	5	Cirrhosis of liver
Le	50	M	84	112	77	105	7	Bowel obstruction (decompressed)
Mo	27	F	88	115	83	107	8	Liver disease (chronic)
Ri	26	M	100	113	70	105	8	Diabetes mellitus (controlled)
St	22	F	72	110	59	101	9	Anorexia nervosa (?)
Ba	35	M		103	56	94	9	Hodgkin's disease
Ba	44	M		127	88	118	9	Cancer of neck
Do	38	M	100	96	62	86	10	Amyotrophic lateral sclerosis
Li	21	M	76	114	50	104	10	Normal
Wi	53	M	80	130	80	119	11	Normal
Ra	26	F		110	78	99	11	Cholelithiasis
Ta	45	M	86	138	88	126	12	Normal
Ma	22	M	76	129	69	117	12	Normal
Lu	49	M	78	150	89	138	12	Psychoneurosis
Fr	28	M	55	112	67	100	12	Normal
Ha	21	M	90	116	65	103	13	Rheumatic fever (?)
Si	19	M	84	121	73	107	14	Normal
Wa	30	M	76	116	68	102	14	Normal
Gu	22	M	65	120	68	106	14	Normal
Ha	60	F		108	54	94	14	Rheumatoid arthritis
Ha	65	M	108	151	96	136	15	Pneumonitis—convalescent
Ne	31	M	80	135	70	119	16	Normal
Si	43	M	66	116	80	100	16	Normal
Ha	30	F	60	109	66	93	16	Cholecystitis
Ga	28	M	60	106	66	90	16	Normal
Wi	36	M	90	127	80	111	16	Multiple sclerosis (?)
Sh	34	F		105	62	89	16	Diabetes mellitus
No	52	M		97	53	81	16	Lung tumor
Ma	43	M	78	132	93	115	17	Normal
Ru	55	F	64	130	82	113	17	Nontoxic goiter
Le	33	M	62	115	70	98	17	Normal
Ta	36	F	70	102	60	85	17	Singulus nervosa
Al	17	M	72	111	68	94	17	Epilepsy
Ke	26	M		118	62	101	17	Upper respiratory infection
Bo	32	M	75	120	73	102	18	Normal
Wi	24	M	58	120	77	102	18	Upper respiratory infection
Be	55	F	72	130	90	112	18	Asthenia
Go	32	M	86	116	56	98	18	Normal
Yo	51	M	78	122	76	104	18	Carcinoma of liver
Ju	25	M	60	118	73	100	18	Upper respiratory infection
Ca	22	M	62	110	76	92	18	Normal
Sy	43	M	68	130	88	111	19	Pancreatitis
Ek	25	F	78	110	62	90	20	Colitis—convalescent
Hu	58	M	78	125	73	105	20	Bowel obstruction (decompressed)
La	35	F	68	97	56	77	20	Asthenia
Re	22	F	52	104	60	84	20	Normal
Me	61	M	72	116	81	95	21	Fever of undetermined origin—convalescent

TABLE I. BLOOD PRESSURE VALUES IN NORMAL SUBJECTS (CONTINUED)

NAME	AGE	SEX	PULSE RATE	BRACHIAL		DIGITAL SYSTOLIC (MM. HG)	BRACHIAL DIGITAL GRADIENT (MM. HG)	DIAGNOSIS
				SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)			
We	35	M	64	120	70	98	22	Normal
McF	22	M	104	148	85	126	22	Normal
Ju	21	M	88	140	69	118	22	Normal
Al	16	F	116	107	65	85	22	Ulcerative colitis (chronic)
Do	30	M	75	110	73	88	22	Normal
Ki	35	M	88	128	74	106	22	Traumatic arthritis of ankle
Te	21	M	72	115	62	92	23	Normal
Al	56	F	76	144	80	121	23	Chronic pancreatitis
Lo	19	M	55	121	70	98	23	Lymphoma (?)
Br	58	M	72	120	81	96	24	Spinal cord tumor
Ke	37	M	84	118	76	94	24	Malaria—convalescent
Ma	59	F	94	125	62	101	24	Nontoxic goiter
Ja	46	M	60	124	70	99	25	Normal
Da	35	M	70	112	78	87	25	Normal
Li	28	M	60	110	65	85	25	Normal
Sw	35	M	68	127	76	101	26	Normal
In	51	M	76	114	54	88	26	Multiple myeloma
Me	23	M	72	120	69	94	26	Normal
Sk	46	M	100	122	76	95	27	Brucellosis
Kr	32	M	75	122	72	95	27	Normal
M	42	M	88	111	76	82	29	Normal
Wh	55	M	67	108	72	79	29	Normal
Be	22	M	98	114	66	85	29	Normal
Ne	48	M	76	129	69	100	29	Peptic ulcer
Wo	42	M	84	149	89	120	29	Progressive muscular atrophy
Os	41	M	72	134	80	104	30	Normal
St	38	M	80	118	84	88	30	Normal
Fr	23	M	68	130	67	99	31	Normal
Averages				119.6	71.5	100.9	18.7	

Average blood pressure values obtained for the entire group were: brachial systolic, 119.6 (range, 96 to 151); brachial diastolic, 71.5 (range, 43 to 96); digital systolic, 100.9 (range, 77 to 138); and brachial-to-digital systolic pressure gradient 18.7 (range, 5 to 31). These data are shown in Fig. 4. The mean values derived for the thirty-four members of this group who were not hospital patients corresponded very closely to the mean values just indicated for the whole group. For this subgroup of the normal subjects, the mean digital systolic pressure was 100.0 and the brachial-to-digital pressure gradient was 20.5 millimeters.

Digital Diastolic Pressures.—Numerous sources of error detracted from the reliability of the values of the digital *diastolic* pressure obtained by the method described. In some subjects the digital pulsations were so weak that the pulse under the cuff could not be felt. In others the fading of pulsations occurred gradually. Also, since this measurement is subjective, the error due to personal equation may be large. Consequently, owing to the probability of large errors, digital diastolic pressures were not included in these studies.

Multiple Readings.—On a number of individuals, five to eight repeated digital systolic readings at two- to five-minute intervals were made. These gave

successive results that usually fluctuated less than 4 mm. Hg (rarely over 6 mm.), and the fluctuations were no greater than the fluctuations of the brachial systolic determinations taken after each digital reading. Rewrapping the cuff caused no significant difference in subsequent readings.

Abnormal Fluctuations.—Four subjects showed such a wide fluctuation in successive digital systolic readings (often accompanied by wide swings in brachial systolic pressure), that only by simultaneous brachial and digital determinations could a correct pressure gradient be established. Since simultaneous readings are impossible with this method, these subjects were not included in the presented data.

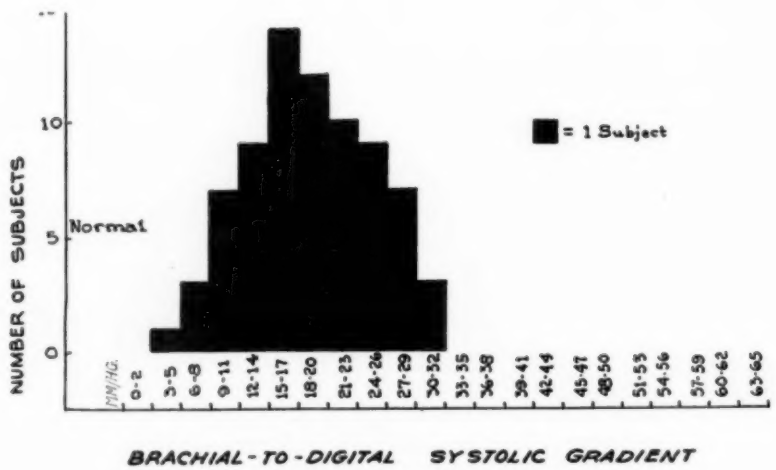

Fig. 4.—Range of brachial-to-digital systolic blood pressure gradients for seventy-five normal subjects.

TABLE II. DAY-BY-DAY COMPARISON OF FLUCTUATION OF BRACHIAL AND DIGITAL SYSTOLIC PRESSURES

Subject D. B.

Day Number	1	2	3	4	5	6	7	8	9	10	11
Brachial	136/83	122/80	121/75	116/68	116/68	111/69	118/68	119/69	115/64	120/72	118/70
Digital systolic	116	112	96	98	99	100	96	95	97	95	96
Brachial—digital gradient	20	10	25	18	17	11	22	24	18	25	22

Subject: J. W.

Day Number	1	2	3	4	5	6	7	8
Brachial	114/69	122/72	127/69	124/75	120/74	121/76	126/77	120/70
Digital systolic	96	100	100	109	98	96	100	98
Brachial—digital gradient	18	22	27	15	22	25	26	22

Repeated Readings on Different Days.—Day-to-day readings demonstrated that some changes occurred both in brachial and digital systolic pressures and in the slope of the gradient between the two. Changes in digital systolic pressure were no greater than those in the brachial systolic pressure. In Table II examples are demonstrated. In D. B., the daily brachial-to-digital systolic pressure gradient ranged from 10 to 25 mm. Hg; in J. W., it ranged from 15 to 27 millimeters. It seems clear that there is a well-defined range of digital systolic blood pressure and it appears to have confines as narrow and distinct as those of the brachial pressure.

DISCUSSION

The described results serve to establish normal values for the digital systolic blood pressure, and for the brachial-to-digital systolic pressure gradient. The mean values obtained for these determinations are similar to those reported by earlier investigators. From our results in a larger series of subjects we have been able to establish well-defined limits for the normal range of the brachial-to-digital pressure gradient.

For reasons already mentioned, the digital *diastolic* pressure has not been included in the presented data. However, the determination may be of value when changes in blood pressure are being observed in a given individual in response to drugs or other stimuli. Under such circumstances the subjective factor is constant.

The value of the systolic blood pressure determined by the technique described is actually a measure of the maximum lateral pressure in the palmar arch artery. When the finger cuff is inflated above systolic pressure the portion of the digital artery between the palmar arch and the border of the cuff will have the same blood pressure as that in the palmar arch with the one exception, namely, that in the digital artery there will be a water-hammer effect caused by the reflection of the pressure pulse against the cuff occlusion. Maltby and Wiggers[20] have demonstrated that the oscillatory rise in pressure resulting from this type of reflected pulse is too transient to force blood under an occluding cuff. Thus, the end point will not appear until the pressure in the cuff is just below the systolic lateral pressure in the palmar arch. Changes observed in the reading of the digital systolic end point actually represent changes in the maximum lateral blood pressure of the palmar arch.

The degree of dilatation of the vascular bed in the particular finger used will not alter this reading since the end point merely represents the passage of blood under the cuff and is not dependent on the rate of blood flow through the finger. Only when the digital artery is so markedly constricted that blood seeps through slowly to the skin will the end point be invalid. Thus, we have found it impossible to determine digital blood pressures in a patient with Raynaud's disease during an attack.

Results of the digital pressure determination on this group of normal subjects show that the digital systolic pressure is an accurate clinical measurement with a well-defined "normal" range. The decrease in systolic pressure between the brachial and digital arteries (brachial-to-digital systolic pressure gradient)

falls within rather narrow limits. The constancy of the digital blood pressure and brachial-to-digital pressure gradient has been demonstrated by repeated determinations at short intervals and by multiple daily readings.

CONCLUSIONS

1. A simple, reliable method for the determination of digital systolic blood pressure is described. The results obtained by this method were as constant as the values for brachial blood pressure obtained by the ordinary auscultatory method.

2. The normal digital systolic pressure ranges from 77 to 138 mm. Hg with an average of 100.9 millimeters.

3. The normal brachial-to-digital systolic pressure gradient ranges from 5 to 31 mm. Hg with an average gradient of 18.7 millimeters.

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THE DIGITAL BLOOD PRESSURE. II. THE BRACHIAL-TO-DIGITAL SYSTOLIC PRESSURE GRADIENT IN HYPERTHYROIDISM

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WHILE determining comparative brachial and finger blood pressure values on patients with a variety of diseases, we have found certain consistent abnormalities in hyperthyroidism that we have not seen described. Our studies have shown that the drop in systolic blood pressure between the arm and finger is significantly greater in patients with hyperthyroidism than in normal subjects.

METHOD

Employing a modification of the principle described by Gaertner[1] in 1899 we recently established normal values for the systolic blood pressure in the finger and for the brachial-to-digital systolic pressure gradient.[2] The literature was reviewed and the method described in detail. Briefly, the apparatus consists of a miniature blood pressure cuff that can be attached to the ordinary sphygmomanometer. The cuff is wrapped snugly about the proximal phalanx of a digit. Any digit will do but for the sake of uniformity we use the middle finger. The finger distal to the cuff is then blanched by wrapping it with a strip of rubber and the cuff is inflated, after which the rubber is removed. As the cuff pressure is lowered, the manometer reading when the first flush of color appears in the blanched end of the finger is the digital systolic pressure. In order to determine the brachial-to-digital systolic pressure gradient the average of two or more digital systolic readings is subtracted from the average of two or more brachial systolic readings. The fluctuations in successive finger systolic pressure readings are of about the same magnitude as the fluctuations in repeated brachial systolic pressure readings. The finger diastolic readings, subjectively determined by cessation of throbbing as the cuff pressure is lowered below the systolic level, are frequently unreliable and therefore have not been included in this study.

RESULTS IN EIGHTEEN PATIENTS WITH HYPERTHYROIDISM

Our results show that the fall of systolic pressure between the brachial and digital arteries is definitely greater in patients with hyperthyroidism than in normal subjects. The normal brachial-to-digital systolic pressure gradient ranges from 5 to 31 mm. of mercury.[2] The average brachial-to-digital systolic pressure gradient for our series of eighteen hyperthyroid patients was 41.7 mm. of mercury.

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The lowest pressure gradient was 12 and the highest 61 mm. of mercury. In Fig. 1 the brachial-to-digital systolic pressure gradient in our group of patients with hyperthyroidism is compared to that of normal subjects as reported earlier.[2] In hyperthyroidism it is seen to be significantly above the normal range.

Table I shows that fourteen patients have gradients above the normal level while four have gradients within the established normal range. Each of the four individuals with a normal brachial-to-digital gradient had been receiving continuous treatment with Lugol's solution or prophlthiouracil for at least eight

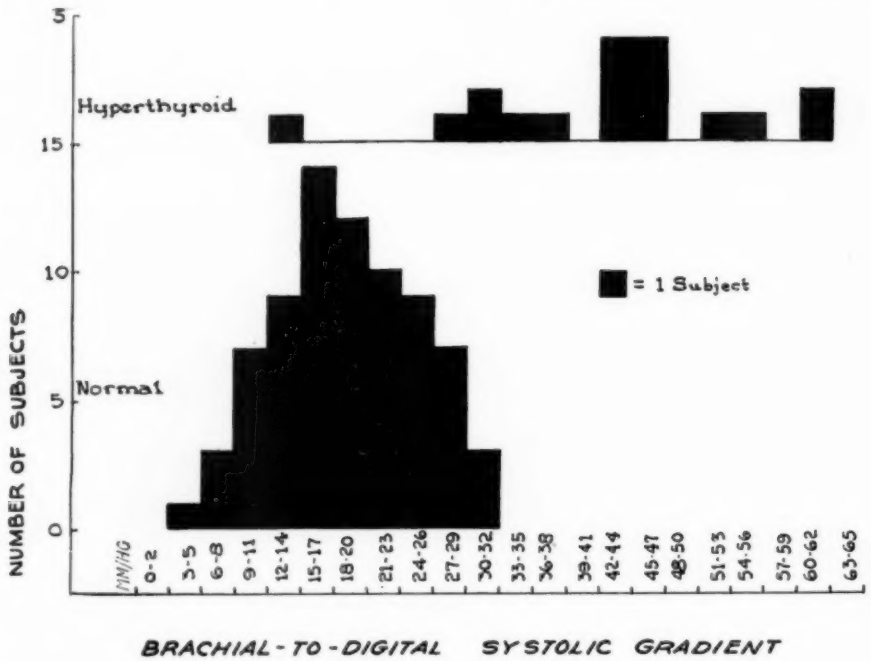

Fig. 1.—Comparison of the brachial-to-digital systolic pressure gradients of eighteen hyperthyroid patients with a group of normal subjects.

days prior to the time our blood pressure determinations were made. In summary then, of the eighteen hyperthyroid patients, the only four with gradients within the normal range were patients who were actively receiving preoperative treatment.

The normal digital systolic pressure ranges between 77 and 138 mm. of mercury.[2] In the present group of patients with hyperthyroidism the digital systolic pressures were nearly all normal, ranging from 72 to 123 mm. of mercury.

GRADIENT CHANGES OCCURRING DURING PREOPERATIVE TREATMENT AND AFTER THYROID SURGERY

Several observations were made on four patients during preoperative preparation with Lugol's solution, or propylthiouracil, or both, and also following

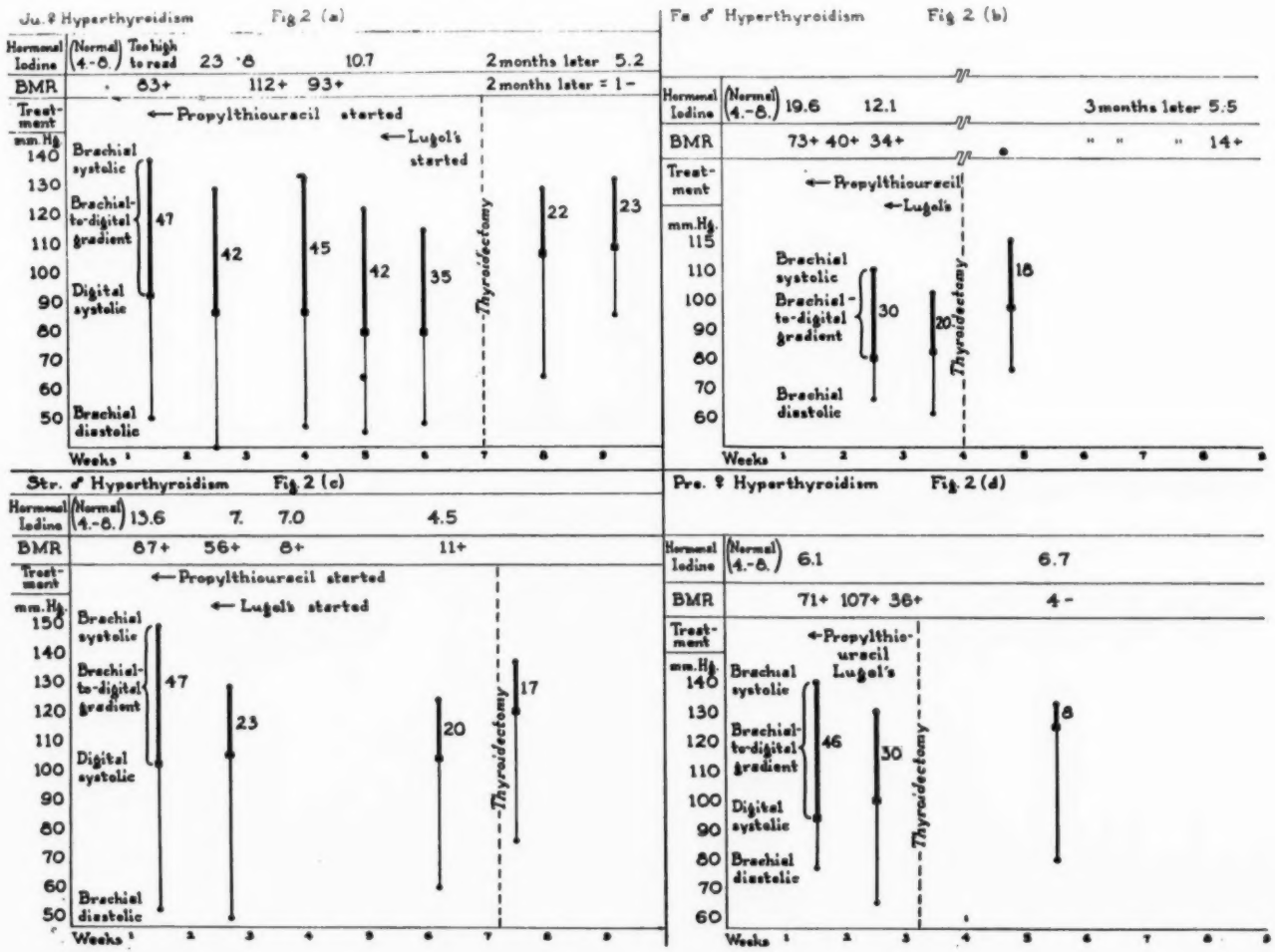

Fig. 2.—Four patients (*a*, *b*, *c*, and *d*) with hyperthyroidism on whom brachial and digital blood pressure determinations were made at intervals. Demonstrates decline in brachial-to-digital systolic pressure gradient during treatment and postoperatively.

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thyroidectomy. Data on these patients are shown in Fig. 2. In each of the four patients there was a decrease of the brachial-to-digital systolic pressure gradient during treatment. The decrease in gradient slope roughly paralleled the fall in basal metabolism rate and hormonal iodine, and the clinical improvement of the patient. In all cases the gradient was normal following operation. Before operation the improved gradient appeared to be produced by a progressive lowering of the brachial systolic pressure without change in the finger systolic pressure. Following operation there was a rise in both brachial and digital systolic pressure concomitantly. As would be expected there was a postoperative decrease in pulse pressure. While the blood pressure changes were no greater than one often finds when making determinations on a subject on different days, the changes were all in a direction which resulted in both a diminution in brachial-to-digital gradient and in a decrease in pulse pressure.

The correlation between the original values for the basal metabolism rate and brachial-to-digital systolic gradient is poor. However, where these two values are high in patients with hyperthyroidism, treatment appears to decrease both toward normal at approximately the same rate.

DIASTOLIC PRESSURE

As mentioned earlier the determination of finger diastolic pressure is subjective and gives no constant results. Furthermore, the brachial diastolic value is also difficult to obtain in patients with hyperthyroidism because of poor definition of sound changes at the diastolic end point. However, it is of interest to note that following thyroidectomy in our four patients, the last phase of the Korotkoff sounds became well defined and the brachial diastolic pressure could be measured as well as in a normal subject. In all four patients the postoperative brachial diastolic pressures were definitely higher than during the preoperative period, and, as would be expected, the pulse pressures were considerably lower.

DISCUSSION

There is ample evidence that increased quantities of blood pass through muscles and skin in hyperthyroidism. Experimentally, Eriksson and Petren[3] found that the feeding of thyroid substance produces increased vascularization due to dilatation and formation of new capillaries in the myocardium and skeletal muscles of guinea pigs. In a quantitative study of cutaneous capillaries, Roberts and Griffith[4] counted the capillaries of an area of skin on the forearm in a group of normal subjects and patients with hyperthyroidism before and after pricking the skin with histamine. They found a far greater increase in capillary count in the normal group after histamine pricking, indicating that almost maximal capillary dilatation was already present in the patients with hyperthyroidism. They also noted that a greater number of capillaries were usually found in members of the hyperthyroid group. Plethysmograph and skin temperature studies have confirmed the clinical opinion that blood flow is increased in the hyperthyroid state. Eichna and Wilkins[5] and Abramson and Fierst[6] found a marked increase in blood flow through the forearm and calf in hyperthyroid patients as

compared with normal persons. Furthermore, Abramson and Fierst found no significant increase above normal in blood flow through the *hand* in hyperthyroid subjects. The hand circulation determinations were in the upper range of their readings for a control group. Stewart and Evans[7] found that the average skin temperature in hyperthyroidism roughly followed the decline in basal metabolism rate after treatment but that the hand temperature dropped a much smaller amount after operation than did the temperature of the skin in the other areas measured. However, they found the average hand temperature in patients with hyperthyroidism to be warmer than normal in all instances. Kirklin and associates[8] described only minor reductions in finger temperature after treatment with Lugol solution and after thyroidectomy. Our observations are in accord with the view that although there may be some increase in circulation to the hand, the increased inflow to the tissues of the forearm is probably more significant. The abnormally widened brachial-to-digital pressure gradient may well be produced by the increased shunting of blood from the brachial-digital arterial thoroughfare into the tissues of the forearm. Since, in the hyperthyroid state, there is an increase in blood volume[9] and cardiac output,[10] sufficient blood still travels into the hand to maintain a high normal blood flow.

Although with treatment the improvement in brachial-to-digital systolic pressure gradient roughly parallels the improvement in basal metabolism rate and hormonal iodine, occasionally there were wide discrepancies in these correlations in individual hyperthyroid patients in the group of eighteen studied (Table I). It is well known that no single test gives an absolute measure of thyroid activity.

Our observations demonstrating a consistently abnormal brachial-to-digital systolic pressure gradient in patients with hyperthyroidism suggest that this determination should be of value not only as an aid in the diagnosis of hyperthyroidism, but also in evaluating the patient's response to treatment and preparedness for thyroidectomy.

SUMMARY

1. The fall in systolic blood pressure between the arm and finger (brachial-to-digital gradient) was studied in eighteen patients with hyperthyroidism. In fourteen of these patients the brachial-to-digital gradient was greater than normal with a range of gradient from 33 to 61 mm. Hg as contrasted with the normal range of 5 to 31 mm. of mercury. A normal gradient was found in the remaining four patients but each of these patients had been under treatment with iodine or propylthiouracil for at least eight days when the determinations were made.

2. The digital systolic pressure was within the normal range.

3. In four of the eighteen patients several determinations were made during the period of preparation for thyroidectomy and postoperatively. In all cases the brachial-to-digital systolic gradient was normal after operation. There was a decrease toward normal of the gradient during the preoperative preparation that roughly coincided with clinical improvement and lowering of the basal metabolic rate with hormonal iodine.

TABLE I. DATA ON EIGHTEEN PATIENTS WITH HYPERTHYROIDISM

PATIENT	AGE	SEX	PULSE	BRACHIAL PRESSURE (MM. HG)	DIGITAL SYSTOLIC (MM. HG)	BRACHIAL DIGITAL GRADIENT* (MM. HG)	DURATION OF TREATMENT†	BASAL METABOLIC RATE	DAYS BETWEEN LAST BMR AND BLOOD PRESSURE STUDIES
Br	39	F	80	108/42	72	36	4 days	+36	21
Ca	43	F	86	148/89	106	42	0	+13	3
Hu	58	F	90	139/55	84	55	0	+30	5
Ra	34	F	85	152/55	107	45	20 days	+57	6
Ni	44	F	100	140/64	80	60	3 days	+41	1
Cla	54	F	114	129/69	87	42	0	+30	1
He	48	F	88	168/76	117	51	6 weeks	+24	1
Sc	36	M	96	144/57	100	44	0	+73	0
Ta	18	F	100	136/52	75	61	?	+16	0
Pr	27	F	104	140/76	94	46	1 day	+71	1
La	24	F	140	140/52	98	42	0	+51	0
Ju	29	F	124	138/50	91	47	0	+83	3
St	33	M	116	149/52	102	47	0	+87	5
Gr	26	F	108	128/54	95	33	0	+36	5
Cle	34	F	80	135/76	123	12	Weeks	+37	1
Wo	62	F	88	125/64	94	31	10 days	+17	0
Fa	43	M	100	110/66	80	30	8 days	+34	0
Ei	35	M	100	127/56	100	27	8 days	+10	2

*Normal gradient ranges from 5-31 mm. of mercury.
†Length of time patient had been receiving Lugol's solution or propylthiouracil or both at the time blood pressure studies were made.

4. The mechanism responsible for the increased gradient in hyperthyroidism is discussed.

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LEAD POISONING

IX. The Failure of Lead Poisoning to Affect the Heart and Blood Vessels

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THE observations recorded in this article are based on the studies of 340 patients with clinical and laboratory evidences of lead poisoning. As indicated in previous articles[1] this group of patients was separated into three subgroups as follows: (1) those having acute lead poisoning; (2) those having chronic absorption of lead with acute toxic manifestations; and (3) those with chronic lead poisoning. All of these individuals developed symptoms of plumbism as a result of occupational exposure. The results of clinical observations,[2a] laboratory studies,[2b] and therapy[3] were previously reported. In the present article the results of the investigations on the effects of lead poisoning upon the cardiovascular and peripheral vascular systems in selected subjects are being added. These studies were performed during the period of active clinical symptoms of plumbism and in the presence of laboratory evidence of abnormal lead metabolism.

In the literature of the past century lead has often been cited as an etiological factor in hypertension and arteriosclerosis. Prior to the introduction by Riva-Rocci[4] of the pneumatic cuff for measuring blood pressure, the arterial tension was estimated by palpation of the larger arteries. Frank[5] stated that palpation of the radial artery in individuals who had plumbism revealed a peculiar firmness and tension. Using the same criterion, Tanqueral de Planches[6] reported that in approximately one-half of the individuals whom he had observed there was a hard pulse. While a full arterial pulse in patients with acute lead poisoning was observed and reported by Hitzig,[7] no such changes were noted in association with chronic lead poisoning. This author attributed the full pulse in patients with acute lead poisoning to the fact that there was a distinct contraction of the arterial musculature with a diminution of the vascular bed. Heubel[8] did not concur in Hitzig's explanation. He found the pulse to be hard during an attack of lead colic and reported that it was not small but on the contrary was full and strong. From the above-recorded observations it is evident that the presence of arterial hypertension in plumbism is based upon assumptions which cannot be considered valid.

After carefully observing workers who were exposed to lead as an occupational hazard for periods of time varying from five to twenty years, Belknap[9] concluded that there was no significant trend toward elevation of either the systolic or the diastolic pressure. In his experimental rabbits, Wirtschafter[10]

noted that the administration of lead did not cause hypertension or any deleterious effects upon the kidneys or the circulatory system. In the report of their observations on the arterial blood pressure of dogs with chronic lead poisoning, Fout and Page[11] concluded that "the administration of lead to dogs over a long period of time and in large amounts does not produce arterial hypertension." Griffith and Lindauer[12] administered lead almost daily for a period of at least thirty days to fifteen healthy albino rats. Four animals survived the completion of the experiment on the eightieth day. All animals that survived forty days were hypertensive. The authors concluded that "chronic lead poisoning can produce hypertension in rats." Teleky[13] was of the opinion that there is no scientific evidence to indicate any increase in the blood pressure accompanying signs of the fresh absorption of lead. The idea that the absorption of lead is attended by increased blood pressure has crept into many mediums, including textbooks, owing, in the opinion of Teleky, to inaccuracy and generalization of compilation of data. Judging from the opinion of others as well as his own Teleky stated: "one would expect at the utmost only sporadic cases of hypertension in individuals exposed to the lead hazard."

In evaluating the question of hypertension in the general population, Master and Dack,[14] using 150 mm. of mercury as the top normal for the systolic pressure and 90 mm. as the normal diastolic pressure, found that the incidence of hypertension in a group of individuals in the age bracket between 40 and 49 years was approximately 32 per cent and in those in the decade between 50 and 59 years it was 42 per cent. In persons in the seventh decade the incidence of hypertension was still higher. It has been assumed that arteriosclerosis is more common among lead workers than in the general population. In a review of the literature, Hamilton[15] makes no mention of any study which would indicate that the incidence of hypertension and arteriosclerosis is any greater in corresponding age groups among those exposed to the lead hazard as compared with similar age groups in persons engaged in any other type of occupation. In a study of 381 lead workers, Mayers[16] did not find that prolonged exposure to lead accelerated the development of arteriosclerosis. Recently, in discussing the subject, Mayers[17] stated: "it is an old medical concept that prolonged exposure to lead accelerates the development of arteriosclerosis, of chronic nephritis, or both. Recent work however has not substantiated this." A comparison of the incidence of arteriosclerosis among sandstone miners and surface miners was reported by Smith.[18] There was little difference. This observer concluded that prolonged exposure to lead might be responsible for a small increase in the incidence of arteriosclerosis among lead miners.

In view of the diverse opinions and the controversy that exists concerning whether or not lead poisoning and chronic lead absorption may have an adverse affect on the cardiovascular and peripheral vascular systems in human beings, special studies were made in a selected group of forty patients. These patients had either acute lead poisoning or developed an acute toxic episode after many years of lead absorption. In all of the subjects studied the clinical symptoms were pronounced and were associated with an abnormal lead metabolism. The investigations of the cardiovascular and peripheral vascular systems and the selected renal function tests were executed at the height of the acute attack.

AGE OF THE PATIENTS AND DURATION OF EXPOSURE

Figure 1 indicates the distribution of the patients according to decade of life. One of the workers was in the second decade, six in the third, eleven in the fourth, fifteen in the fifth, five in the sixth, and two in the seventh. Only six of the patients (15 per cent) were under 30 years of age. Nine were exposed to the lead

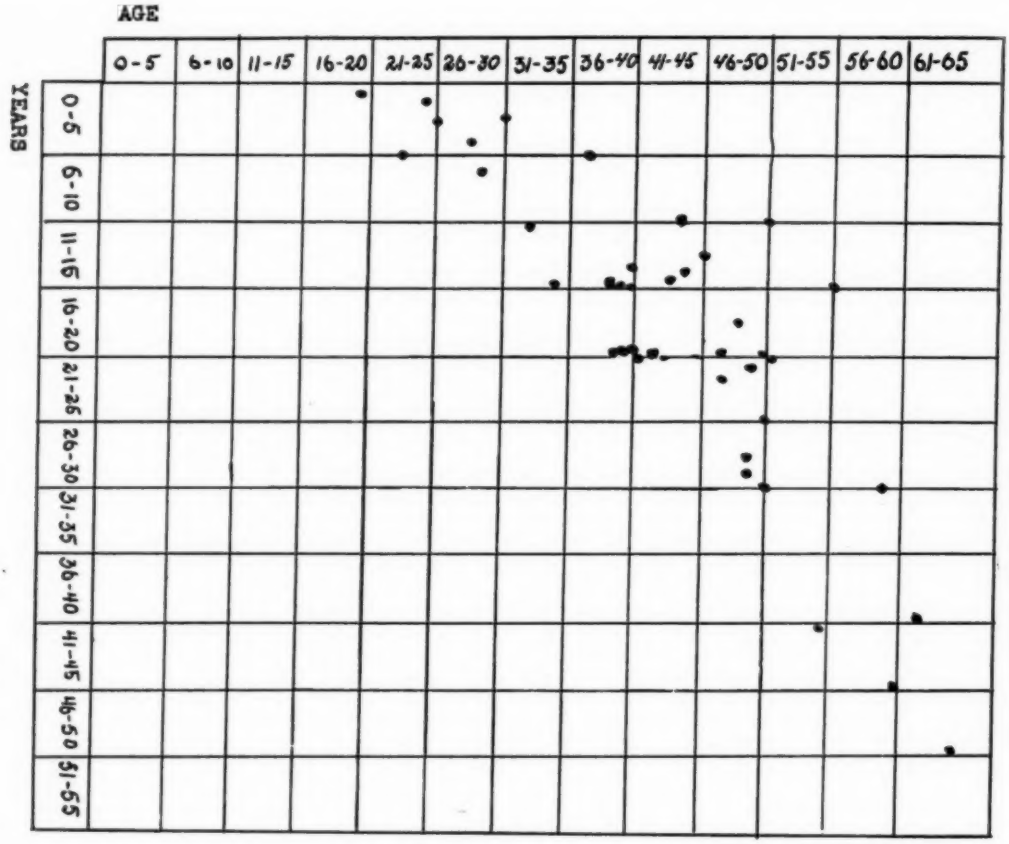

Fig. 1.—Distribution of patients in respect to decade of life and years of occupational exposure.

hazard for less than ten years. The remainder were exposed for from ten to fifty years. Three of the patients were women; two were in the third decade of life and the third was in the fourth. These women developed lead poisoning due to the inhalation of lead fumes. The men had been employed as printers, battery burners, and riveters as indicated in Table I. Thirty-two (80 per cent) of the group had been exposed to the absorption of lead for more than ten years. The longest exposure occurred in a painter 63 years of age who had been working in the industry for fifty years.

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO TYPES OF OCCUPATIONAL EXPOSURE

TYPES OF OCCUPATIONAL EXPOSURE	NUMBER
Painters	17
Riveters	16
Printers	2
Smelters	4
Battery workers	1

EFFECT UPON CARDIOVASCULAR SYSTEM

Of these forty patients studied (Table II), examinations of the heart revealed normal findings in thirty-nine. One patient had rheumatic heart disease. There were no findings to indicate that the pre-existing rheumatic heart disease was in any way affected by the absorption of lead and the attack of acute lead poisoning. Teleroentgenograms were made in 36 of the patients. The cardiac measurements were normal. In thirty-seven patients, electrocardiograms were made. Thirty-six of the tracings were normal. Premature ventricular contractions which were present in one patient disappeared within a few weeks after the patient was removed from the exposure. Three patients had transient hypertension which lasted two to three weeks. These three patients did not have physical examinations prior to the onset of the acute attack of plumbism. With the removal from the occupational hazard and with the subsidence of the clinical manifestations of the acute episode of lead poisoning the blood pressure returned to normal and remained so. It was felt that one was justified in concluding that the paroxysmal or transient hypertension was due to the acute lead intoxication although rest from work may have been a large factor in its termination. In a subsequent article the blood pressure findings in this group will be presented in greater detail.

TABLE II. EFFECT UPON CARDIOVASCULAR SYSTEM

	NUMBER OF PATIENTS	RESULTS	
		NORMAL	ABNORMAL*
Physical examination of heart	40	39	1 (R.H.D.)
Fluoroscopy	40	39	1 (R.H.D.)
Teleroentgenograms	36	36	0
Electrocardiograms	37	36	1 (P. V. C.)
Blood pressure	40	37	3

*R.H.D., rheumatic heart disease; P.V.C., premature ventricular contractions.

EFFECT UPON PERIPHERAL VASCULAR SYSTEM

Observation of the retinal vessels were made in fourteen patients (Table III). None of the eye grounds revealed abnormalities of the vessels. There were no hemorrhages or evidences of either old or recent exudates. The Hines-Brown

test was performed on nineteen patients. It failed to reveal evidence of a hyper-reactor. The Landis test was performed on twelve patients. All showed a normal vasomotor response. The oscillometric studies on the major vessels of twenty-one of these patients revealed normal patency of the vessels of the upper as well as the lower extremities.

TABLE III. EFFECT UPON PERIPHERAL VASCULAR SYSTEM

TYPE OF EXAMINATION	NUMBER OF PATIENTS	RESULTS
Eye grounds	14	Normal vessels; no hemorrhages; no exudates
Hines-Brown test	19	No hyper-reactors
Landis test	12	Normal vasomotor response
Oscillometry	21	Normal patency of major peripheral vessels

EFFECT UPON RENAL FUNCTION

Repeated urinalyses in this group of forty patients acutely ill with lead poisoning revealed no abnormal chemical or microscopic findings. The selected renal function tests revealed essentially normal findings (Table IV).

TABLE IV. RESULTS OF RENAL FUNCTION TESTS

PROCEDURE	NUMBER OF PATIENTS	RESULTS
Urinalyses	40	No abnormal chemical or pathological elements
Dilution and concentration test	34	Good range of specific gravity; normal day-night ratio
Blood chemistry:		
Urea nitrogen	16	
Creatinine	12	Within normal limits
Nonprotein nitrogen	12	
Urea clearance test	31	35-50 c.c. of blood cleared of urea per minute
Phenolsulfonphthalein test	28	Normal amount (60-80%) of dye excreted in two hours

SUMMARY

A variety of studies were performed in 340 patients who had lead poisoning. These patients were observed at various intervals over a period of ten years. Special studies including the cardiovascular and the peripheral vascular systems as well as renal function studies were made in a selected group of forty patients who had pronounced clinical symptoms of acute lead poisoning and who in some instances had pronounced and disabling neurological complications. Studies of the peripheral vascular system did not reveal any findings to indicate any state of vascular spasm or any other change in the peripheral vessels. The size of the heart was not abnormal as ascertained either by physical examination or by teleroentgenography. There were no electrocardiographic abnormalities noted. In approximately 3 to 4 per cent of the entire group of 340 patients

there was a hypertension, transient in nature, which was present for a brief interval during the acute episode of lead intoxication. This transient hypertension was evident during the height of the clinical symptoms and during the period of abnormal lead metabolism. The blood pressure in this group returned to normal following removal of the patient from the occupational hazard and remained normal. The blood pressure in the entire group was essentially the same as that usually present in similar age groups irrespective of occupation. On the basis of these investigations it is evident that the absorption of lead does not have an adverse effect on the cardiovascular or the peripheral vascular systems.

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Clinical Reports

SHORT PAROXYSMS OF TACHYCARDIA DUE TO RECIPROCATING RHYTHM

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THE application of an appropriate electrical stimulus to the heart of the ray and of the frog can produce a peculiar rhythm, in which the contractions of the auricle and ventricle succeed one another alternately, at approximately even intervals, each contraction seeming to depend on a stimulus produced in the opposing chamber. This phenomenon can continue for an indefinite period of time and may be stopped by a new electric stimulus applied either to the auricle or to the ventricle.

Mines,[10] who discovered this curious phenomenon in 1913, termed it "reciprocating rhythm" and admitted that the original stimulus, meeting some part of the conducting A-V fibers in refractory condition, was transmitted only by those fibers which had already recovered. When the stimulus reached the opposing chamber and produced its contraction, the fibers which originally were refractory ceased to be so while, on the other hand, those which had conducted the stimulus had not yet recovered. The activation returned thus by the other path to the original chamber, the phenomenon repeating itself indefinitely. In the hearts of fish and batrachians, the A-V union paths are very wide and the process is easily produced[16] but in mammals these paths are reduced to a narrow bundle and the conditions are different. In spite of this, Scherf and Shookhoff[14] have been able to provoke, in the dog, ventricular extrasystoles with retrograde conduction to the auricles, and on certain occasions the stimulus returned again to the ventricles, provoking another contraction. They designated this phenomenon, "returning extrasystoles" (Umkehrextrasystolen).

In certain circumstances, a similar phenomenon can occur in human beings. In A-V (nodal) rhythm, the retrograde conduction to the auricles can be slower than the anterograde to the ventricles (the negative P wave follows the QRS complex) and, occasionally, when the stimulus reaches the auricles, the conducting fibers have completely recovered and the activation wave may return to the ventricles, provoking a new ventricular contraction. The first to observe this phenomenon were White,[17] Gallavardin and Gravier,[5] and Drury.[3] The last mentioned, connecting it with the experiences of Mines,[10] named it "reciprocal

beating." White,[17] Jones and White,[7] Fogelson and Schewlagina,[4] Blumgart and Gargill,[1] Dock,[2] Levin,[9] and others have published reports of new observations on reciprocal rhythm in patients with A-V rhythm and White has fixed the electrocardiographic pattern which characterizes it, i.e., a negative P wave sandwiched between two approximately equidistant ventricular complexes.

On certain occasions the reciprocal rhythm repeats itself with fair regularity and sets up a curious bigeminy, as in the observations of Jones and White;[7] Gravier, Froment, and Guiran[6]; Fogelson and Schewlagina[4]; and Perelman and Miller[12] (in the observations of Perelman and Miller this is doubtful).

The ventricular contraction which initiates the reciprocal rhythm ought not to originate necessarily in the A-V node, although this seems to be the site of origin most frequently. Langendorf, Katz, and Simon[8] published the report of a case in which ventricular extrasystoles were conducted retrogradely to the auricles and were followed by a new ventricular contraction, originated by a reciprocal rhythm, as in the experimental conditions of Scherf and Shookoff.[14] In a patient with partial A-V block of type 2/1, reported by Wolferth and McMillan,[18] in certain instances, after a normal sinusal contraction, a negative P wave appeared and was followed by a new ventricular contraction.

In all these observations, nevertheless, the reciprocal rhythm did not persist and the second ventricular contraction was not followed by another retrograde auricular contraction, and therefore the phenemonon, though similar to, was not identical with that observed by Mines.[10] Dock[2] establishes a difference between the experimental reciprocating rhythm and the clinical reciprocal, in that the first continues indefinitely and the second does not.

In 1945 Naim[11] reported an instance in which the electrocardiogram showed the presence of reciprocating rhythm in a patient suffering from attacks of paroxysmal tachycardia of some hours' duration. In the free intervals there was often a QRS complex following a normal sinusal P wave, followed in its turn by a negative P wave. This retrograde auricular contraction was most often blocked but eventually provoked a new ventricular contraction. The fluctuating movement could continue a long time, thus producing a tachycardia of 140.

The patient seen by us showed considerable resemblance to Naim's, even though her paroxysms of tachycardia were of much shorter duration. There were, in addition, certain peculiarities which made the case of outstanding interest.

CASE REPORT

The patient was a single woman, 24 years old, whose previous record was devoid of interest. There was no history of diphtheria, rheumatism, tonsillitis, or scarlet fever. One year before our examination a physician told her that she had "arrhythmia" and since then, whenever her pulse was taken, which it was very frequently, it was found to be irregular. It appeared, according to the patient, very often to consist of two beats close together, continued for a long interval. She was anxious about her trouble but there were no subjective complaints.

The clinical examination, apart from the arrhythmia, revealed no abnormality. The blood pressure was 135/80, there was neither albuminuria nor glucosuria, and the x-ray examination showed the heart to be normal in size and shape. The cardiac rhythm seemed to be of two frequencies, one slow and the other more rapid. The first was very often bigeminal and at other times simply very slow, apparently because of the disappearance of the second element of the bigeminal rhythm. The rapid rate occurred in cycles of six to eight regular beats. At times, after slight

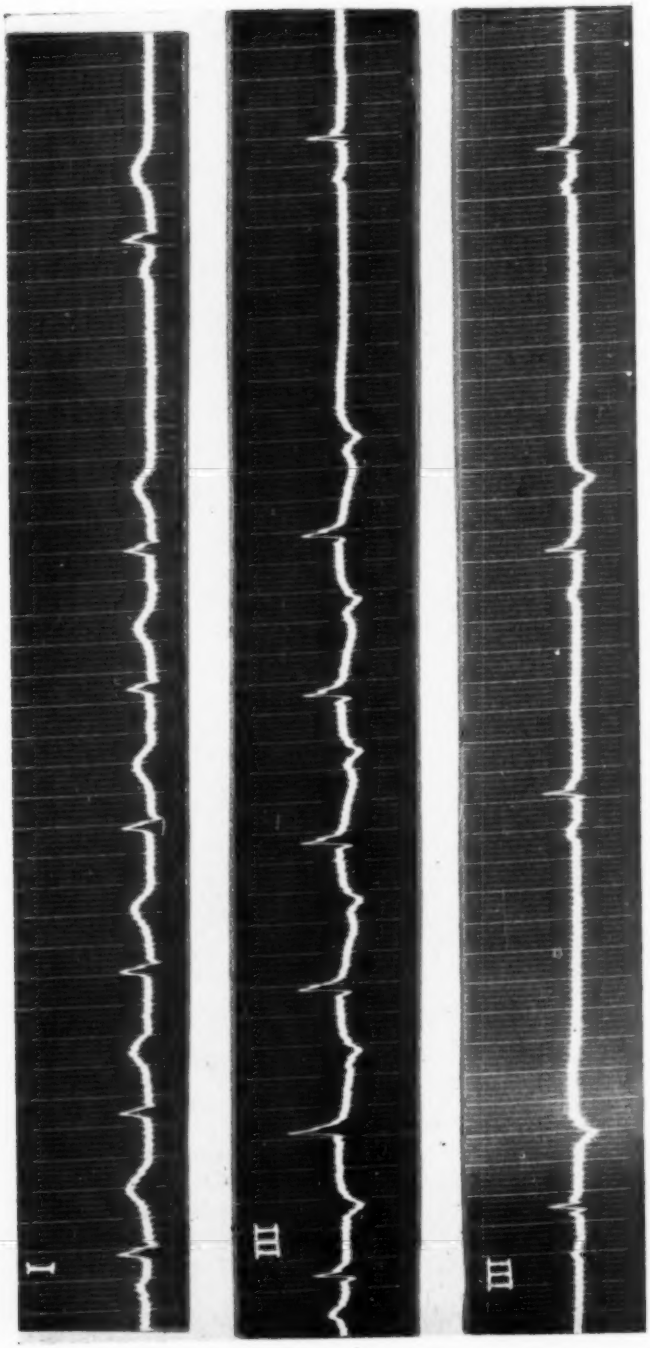

Fig. 1.—Leads I and III of electrocardiogram. Time intervals equal 0.1 and 0.02 second. (See text.)

exertion, a tachycardia of longer duration was obtained; on other occasions, however, the rhythm did not appear to be affected by effort.

Electrocardiographic Records.—In Lead I (Fig. 1) a fragment of tachycardia (at 127 per minute) has been recorded. It consists of a QRS-T group of normal appearance, preceded by a positive P wave (P-R interval = 0.14 second) and five QRS-T groups, very similar to the first, among which no P waves can be clearly recognized. After a pause of 1.02 seconds a QRS complex of sinusal origin follows (P-R interval = 0.12 second).

In Lead II (Fig. 2, in which the three fragments are consecutive records), groups of ventricular complexes (four to six) have been recorded, separated by very slightly irregular intervals (e.g., in the third fragment, the first R-R interval is 0.47 second and the third, 0.51 second). Each one of these groups begins with a positive P wave, followed by a QRS complex (P-R interval = 0.14 to 0.15 second). Immediately after this a sharp negative wave appears, which deforms the T wave and is repeated after each QRS complex except at the end of the cycle. Each time this wave appears to move farther away from the preceding QRS complex and to approach more closely the following one. Sinusal contractions, corresponding to a heart rate of 81 per minute, have been recorded at the end of the curve.

In Table I, the different times in hundredths of a second are shown. The interval R-X (negative wave) was measured from the beginning of the first deflection of the QRS complex to the end of the negative wave which follows, and the X-R from the beginning of the later to the beginning of the following QRS complex.

TABLE I. TABULATION OF INTERVALS IN SECONDS

P-R	R-X	X-R
0.14	0.30	0.26
	0.34	0.20
	0.40	0.17
0.14	0.29	0.25
	0.35	0.20
	0.39	0.18
	0.40	0.16
0.15	0.29	0.23
	0.36	0.20
	0.40	0.18
	0.40	0.20
	0.38	0.19
0.15	0.29	0.23
	0.36	0.20
	0.39	0.20
	0.41	0.16
0.14		
0.15		

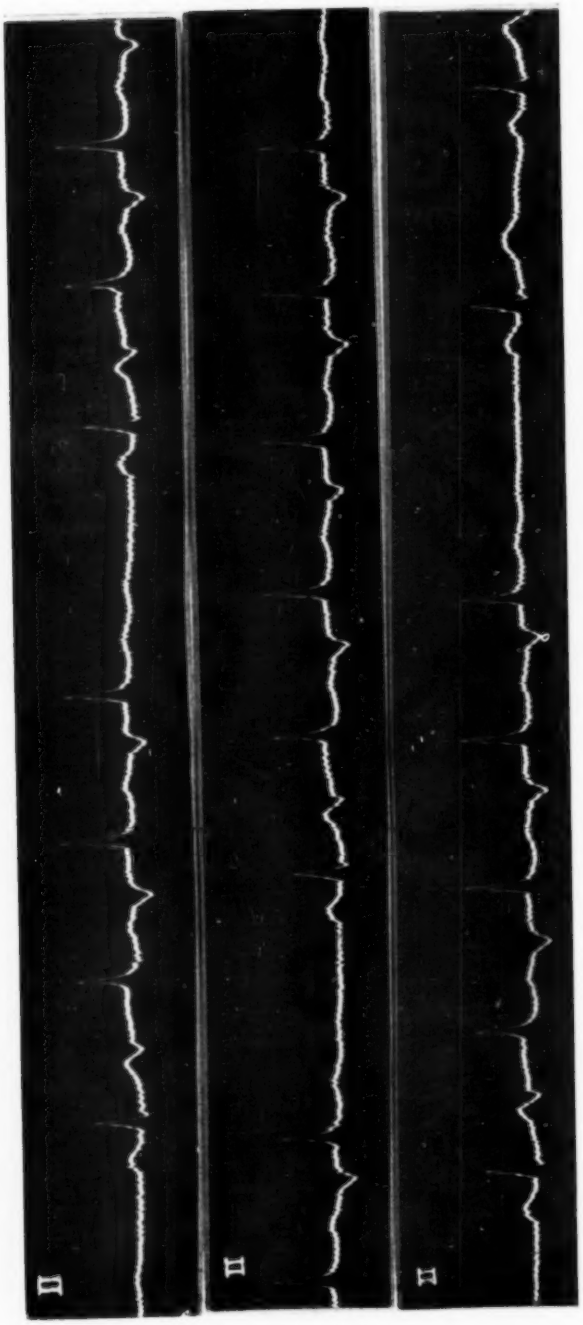

Fig. 2.—Lead II of electrocardiogram. (See text.)

As the table shows, each time a QRS group follows a negative P wave with an interval shorter than 0.20 to 0.18 second, it is not followed by a similar P wave and the cycle is interrupted. On the other hand, there is a certain relation between the time which separates the negative P wave from the ventricular complex which precedes it and the one which follows. The first interval shortens in proportion as the other lengthens.

In Lead III (Fig. 1, the two fragments of which are continuous records) a similar cycle has been recorded but, contrary to what happened in Lead II, it ends with a negative P wave. Next, and after a pause of 1.31 seconds, four QRS groups follow, each of them preceded by a positive P wave (P-R interval = 0.14 to 0.15 second) and every second one of them followed by a negative P wave (R-X intervals of 0.32 and 0.32 second), which remains blocked. The pause which follows the negative P wave is longer than that which precedes it, but it is not compensatory.

In Lead CR_1 the cycles recorded are similar to those in Lead II, though in this lead all the P waves are positive, those in the middle being narrower and sharper than those at the initial phase of the period (Fig. 3).

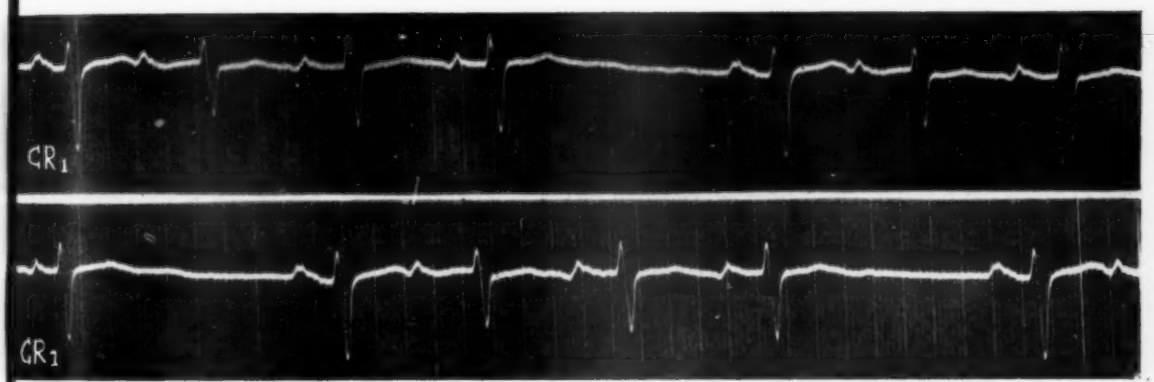

Fig. 3.—Lead CR_1 of electrocardiogram. (See text.)

COMMENTS

We believe that those electrocardiograms are to be interpreted as typical of reciprocating rhythm. The retrograde conduction to the auricles becomes more difficult each time until finally it is stopped, and as a result of this, as the anterograde stimulus is produced later each time, the A-V paths are found more permeable and less time is required to reach the ventricles again. This double mechanism explains why reciprocal rhythm is not indefinitely prolonged.

The progressive slowing-up of the retrograde ventricle-auricle conduction is not an unusual occurrence (White,[17] Dock,[2] Gallavardin and Gravier,[5] Drury,[3] and others); Wolferth and McMillan[18] reported a case which demonstrated this same type of retrograde conduction. Some authors believe that the auricular contractions that are produced following a ventricular systole, originated in the A-V node or in the specific system of the ventricles, are not the result of retrograde transmission of the electrical stimulus but are due to a mechanical stimulus of the auricles produced by the contraction of the ventricles. The patient studied by Wolferth and McMillan (first case) had a complete heart block. Each idioventricular systole was followed by an extrasystole, in this way originating a bigeminal rhythm. Very often, following each QRS group, a negative P wave

appeared, the first R-P interval being 0.18 second and the second 0.24 second. It could be admitted that the mechanical conditions were not the same during the first ventricular contraction as during the second and that this justified the difference in the time observed, but this explanation is invalidated by the fact that sometimes only the second QRS complex was followed by a negative P wave and, in this case, the R-P interval was 0.18 second. Evidently the retrograde conduction was more difficult after the passage of the first stimulus. This observation thus confirms the possibility of retrograde conduction, a fact already postulated by one of us (J.C-A.) sometime ago.

It is interesting to speculate on the reasons why in our patient, as in Naim's,[11] the reciprocal rhythm persisted over periods of varying length. The majority of the observed instances of reciprocal rhythm have been in patients with organic heart disease (Drury,[3] Jones and White,[7] Blumgart and Gargill,[1] Wolferth and McMillan,[18] and others); in these cases it could be postulated that the lesions affected the node of Aschoff-Tawara and the bundle of His, producing changes in excitability appropriate for the establishment of the phenomenon. In Naim's case, as in ours, the presence of such lesions could not be assumed. According to the law of the absolute refractory period it may be assumed that the stimulus was not conducted twice by the same path (Scherf and Boyd[13]) and, therefore, the existence of an anomalous communication, possibly congenital in origin, between ventricles and auricles, capable of conducting the excitation in a sense the inverse of normal, must be admitted.

SUMMARY

A case is herewith reported of a woman 24 years old who, without obvious heart disease, has revealed an unusual arrhythmia consisting of short paroxysms of tachycardia due to reciprocating rhythm, each one initiated by the normal sequence of auricular and ventricular contractions followed by retrograde auricular stimulation.

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AURICULAR TACHYCARDIA WITH AURICULOVENTRICULAR BLOCK OF 12 YEARS DURATION IN A 16-YEAR-OLD GIRL

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THE occurrence of paroxysmal rapid heart action during infancy and childhood is not unusual and the attacks usually are short lived. In patients on whom electrocardiograms have been made, parosyxmal auricular tachycardia with 1:1 ventricular response is more frequent and auricular flutter and auricular tachycardia with A-V block are less frequently encountered. It has been considered that in patients with flutter the rapid heart action is usually of longer duration than in those with paroxysmal auricular tachycardia. Sherman and Schless[6] reported a patient who had continuous flutter from the age of 2 to 5 years with reversion to normal rhythm. Reports of auricular flutter with persistence for many years in older patients are in the literature.

Since 1912 there have been reported patients having auricular tachycardia with A-V block, usually 2:1, and, in 1943, Barker and co-workers[3] called attention to the condition by collecting seventeen previous reports and adding eighteen of their own. Of these thirty-five patients, twenty-three had organic heart disease and most of them were adults. Also, in 1943, Decherd and associates[4] reported on auricular tachycardia with A-V block and all of their patients either had heart disease or were digitalized. These authors summarized the criteria for differentiating between auricular flutter and auricular tachycardia with A-V block. They mentioned the difficulties of coming to a decision regarding the type of rhythm. The auricular rate is usually more rapid in cases of flutter and usually the arrhythmia is of longer duration. Carotid pressure is more apt to stop auricular tachycardia and to slow the ventricular response in flutter.

In 1944, Evans[8] studied twenty-seven consecutive patients having auricular tachycardia with A-V block, paying particular attention to Lead CR_1. The auricular rates in these patients varied from 210 to 496 and even at the rapid rates a return of the auricular wave to the isoelectric line was noted in CR_1. The patients with more rapid rates seemed to recover more quickly than those with slower rates. Evans felt that there has been much confusion in attempting to differentiate between auricular flutter and auricular tachycardia and gave sound reasoning which suggests that they may be the same, namely, a circus movement involving the specialized tissue of the auricle. The case reported may be classed as persistent supraventricular tachycardia with A-V block.

CASE REPORT

The patient is a 16-year-old girl who was apparently normal at birth. Her mother recalls having noted forceful beating of the heart during the first three years of life and soon after the age

of 3 years the child began to have unusual dyspnea. She could not play actively and signs of congestive heart failure became evident. At the age of 4 years (1936) she was hospitalized under the care of Dr. T. Campbell Goodwin at Johns Hopkins Hospital. The child was found to have congestive heart failure with edema, an enlarged liver, and a dilated heart. An electrocardiogram on August 25, 1936 (Fig. 1) showed what was interpreted as auricular flutter with 1:1 response, the auricular and ventricular rate being 200 per minute. One week later 2:1 block was noted (Fig. 2). The auricular rate was 200 and the P waves were inverted in Leads II and III. The patient was digitalized and improved rapidly so that at the end of one month she was discharged free of symptoms but with a persisting auricular tachycardia.

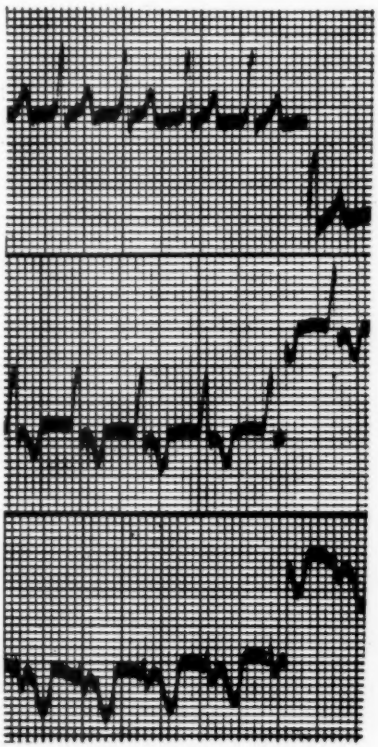


Fig. 1

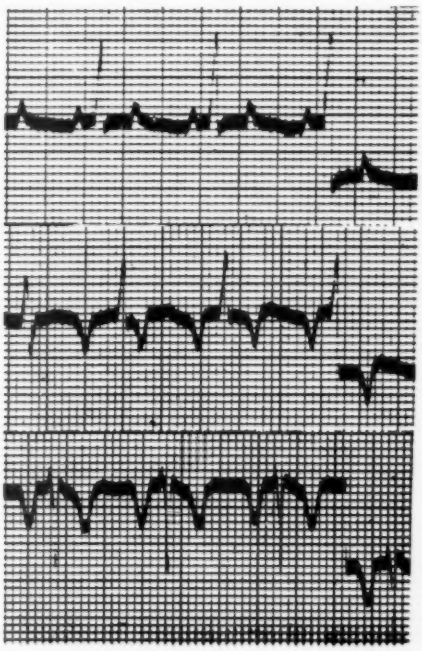


Fig. 2

Fig. 1.—Electrocardiogram of Aug. 25, 1936. Auricular rate 190 to 200 with 1:1 ventricular response.
Fig. 2.—Electrocardiogram of Aug. 31, 1936. Auricular rate 190 to 200 with 2:1 block.

She was seen regularly during the next ten years by Dr. Goodwin and she did well with fairly normal activity unless she left off digitalis, in which case she would have troublesome tachycardia and fatigue. Electrocardiograms when taken, usually showed the auricular rate to vary between 190 and 240 with a 2:1 block. But on Jan. 4, 1937, an electrocardiogram (Fig. 3) showed a tachycardia with a different supraventricular focus and an occasional extrasystole from even another focus. In two days the electrocardiogram had returned to the former type and on two consecutive days in July, 1937, the auricular rate was recorded as 136 with an irregular ventricular response. These tracings are not available.

In August, 1947, the patient came under the care of the author. She was a thin, adolescent girl whose main complaint was palpitation which was aggravated by exertion. She had other symptoms due to her anxiety, in part a result of her close maternal supervision. She had not taken digitalis in several months. She had no evidence in the history, nor signs on physical examina-

tion, of congestive heart failure. She could ride a bicycle with mild dyspnea but never had been allowed to swim. On examination, the heart seemed normal except for a steady rate of about 120 beats per minute. The first heart sound was split. Blood pressure was 100/60. No murmurs were present. Fluoroscopic examination showed an elongation of the left ventricular segment but otherwise no enlargement could be demonstrated. An electrocardiogram (Fig. 4) taken Aug. 9, 1947, showed an abnormal auricular mechanism. The rate was 220 per minute and

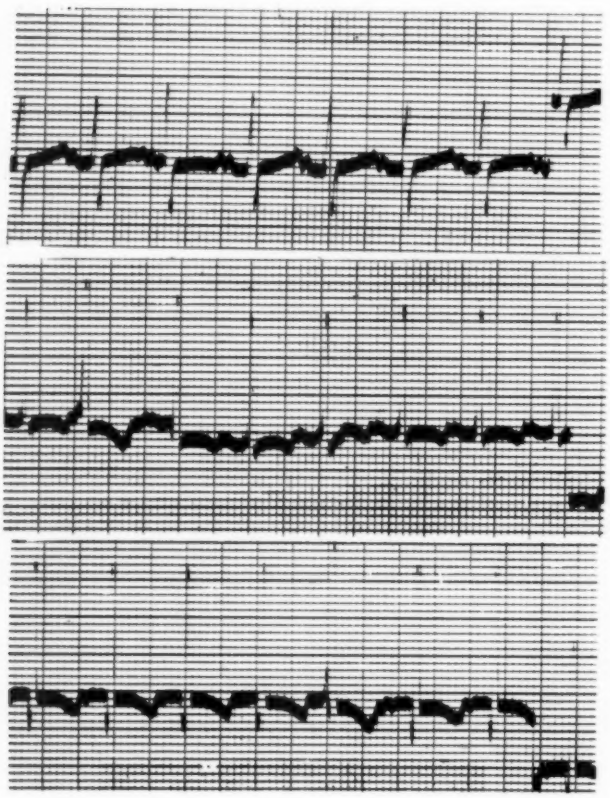


Fig. 3

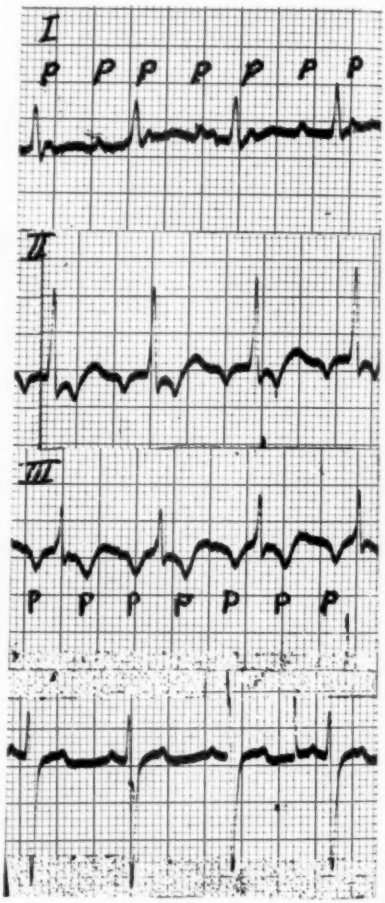


Fig. 4

Fig. 3.—Electrocardiogram of Jan. 4, 1937. Auricular tachycardia with different type P wave. Rate 140 with 1:1 response. Also supraventricular extrasystoles are present.

Fig. 4.—Electrocardiogram taken on Aug. 9, 1947, showing auricular rate 220 with 2:1 A-V block. Patient receiving no treatment.

2:1 A-V block was present; the auricular waves were inverted in Leads II and III. There was a complete return of the auricular waves to the isoelectric line between beats and this has remained a constant finding. The rapid rate was not influenced by carotid sinus pressure. In an attempt to break the tachycardia the patient was given quinidine, 9 grains daily, for one week. The only change in the electrocardiogram was a slight drop in auricular rate to 214 and a prolongation of the P-R interval to 0.24 second (Fig. 5,*A*). She was then hospitalized and given quinidine sulfate, 33 grains in twenty-four hours, with no change. Digitalization was done rapidly with a

drop in ventricular rate to about 84 and an irregular ventricular rhythm (Fig. 5,*B*). The auricular rate remained 208 beats per minute. The patient felt much improved with the heart responding in this manner and she was sent home to continue on quinidine sulfate, 18 grains daily and Purodigin, 0.2 mg. daily. Quinidine, 18 grains a day, was continued with digitalis and a week later (Aug. 26, 1947), the auricular rate was 208 and ventricular response regular at 104. Now carotid sinus pressure did cause an irregular and slower ventricular response. Fig. 6 shows a continuous tracing. This routine of digitalis and quinidine was continued with the patient active and comfortable, the auricular rate constant at 208, and the ventricular response irregular and variable at 80 to 100 beats per minute. On Nov. 20, 1947, quinidine was stopped and this made no difference in her feeling of well being nor in the electrocardiogram. The auricular rate was not always exactly the same but varied between 208 and 220. The patient was kept on digitalis with no quinidine and she was comfortable physically. She would occasionally complain of faintness without loss of consciousness and at these times her pulse was recorded as quite slow by her mother. The lowest recorded rate on an electrocardiogram was 70 per minute.

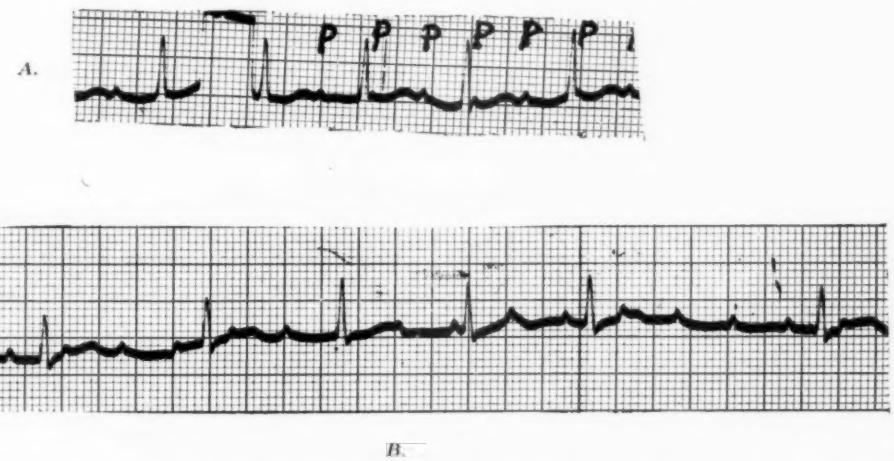


Fig. 5.—*A*, Lead I of tracing taken Aug. 19, 1947. Patient on quinidine sulfate, 9 grains daily. P-R interval 0.24 second. Auricular rate 214, 2:1 block. *B*, Lead I, Aug. 26, 1947. Patient on quinidine sulfate, 24 grains a day and digitalized. Auricular rate 208, ventricular rate irregular at 84 beats per minute.

For six months the patient was followed at three or four week intervals with no particular change until June 9, 1948. On this occasion the patient felt no differently but the electrocardiogram showed a change of auricular rate to 136 per minute; the ventricular response was irregular at about 80 to 90 beats per minute (Fig. 7). The auricular complex was of the same character as that in previous recordings with inversion in Leads II and III. The ventricular rate was increased by exercise, uninfluenced by carotid sinus pressure, and in a resting phase after exercise the A-V block became a steady 2:1. Again on July 1, 1948, the auricular rate was still found to be 136 and on this occasion there was a 1:1 ventricular response with a varying P-R interval (Fig. 8). In August, 1948, the electrocardiogram showed a return of the auricular rate to 210 with irregular ventricular response and it remains so in April, 1949.

Although there were intervals as long as six years during which this patient was not observed, her history strongly suggests that the abnormal rhythm has never returned to a normal sinus rhythm. The patient carries on an active life except for some anxiety and emotional tension and this has lessened as she has done more physical exercise. It seems unlikely that reversion to normal sinus

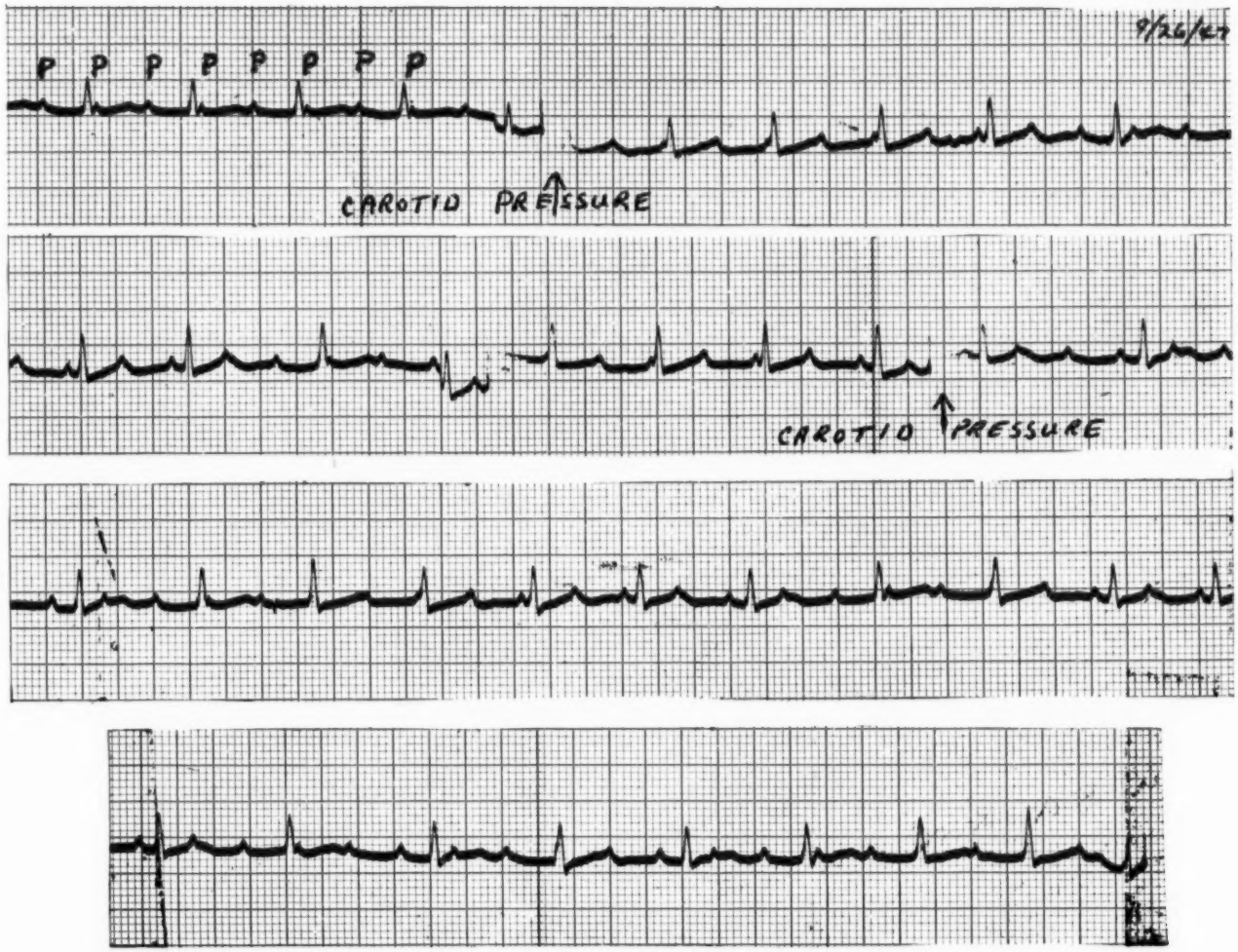
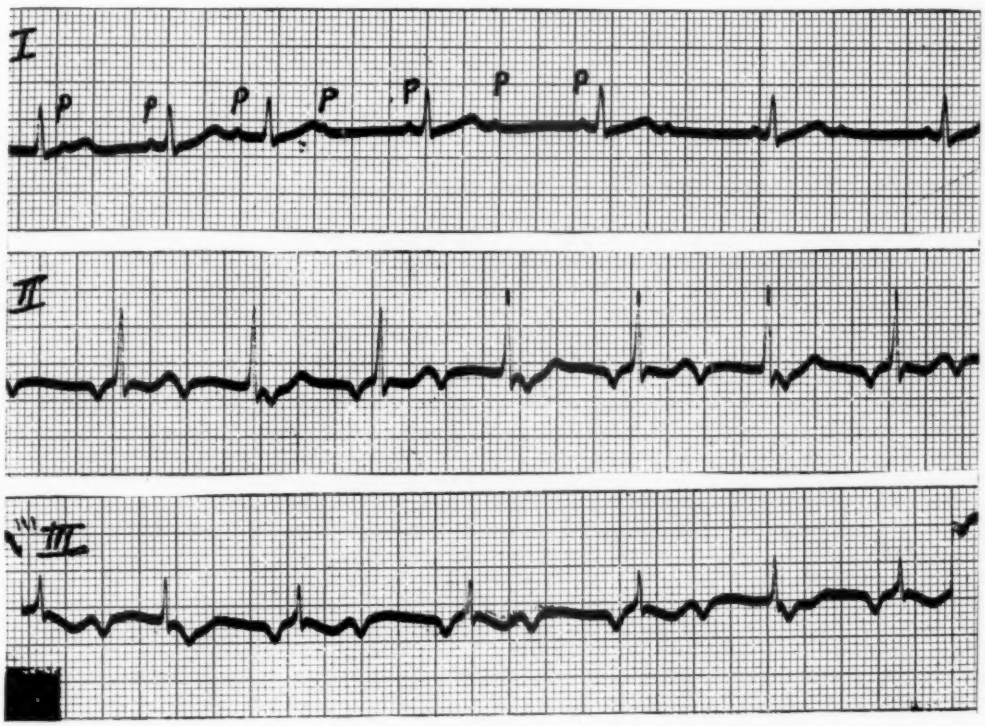


Fig. 6.—Electrocardiogram showing effects of carotid sinus pressure in slowing ventricular response. Patient on quinidine and digitalis at the time. The same effect was obtained while she was on digitalis alone (Lead I).



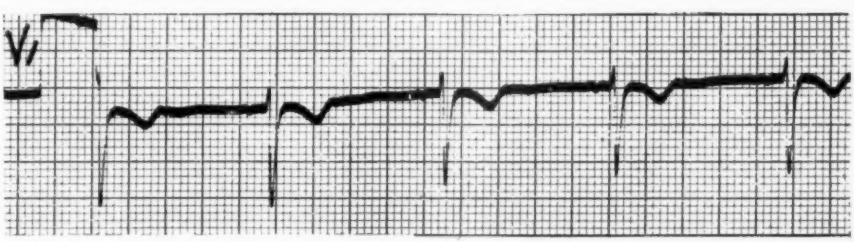


Fig. 7

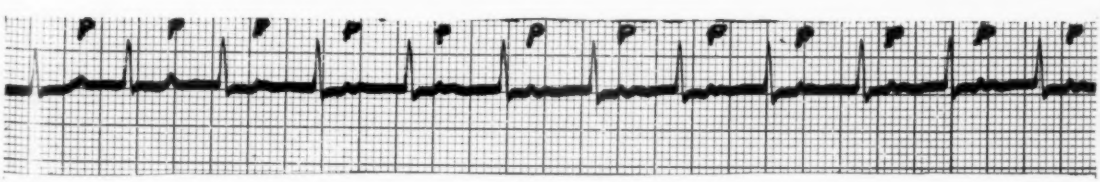


Fig. 8

Fig. 7.—Electrocardiogram of June 9, 1948 showing a change in auricular rate to 136 with no change in the auricular complex. Ventricular response irregular. Patient on digitalis.

Fig. 8.—Continuous tracing of Lead I of electrocardiogram of July 1, 1948, showing the tachycardia with an auricular rate of 136 and partial A-V block, the P-R intervals being 0.24 to 0.32 second with 1:1 response. Patient on digitalis.

mechanism will take place after these thirteen years although such has usually occurred in similar patients with auricular tachycardia which develops in childhood.

SUMMARY

1. Auricular tachycardia with A-V block and auricular flutter in children have not been reported often and at times they have been hard to differentiate. Evans[8] has presented evidence to suggest that they are essentially the same mechanism.

2. An instance of persistent rapid heart action of thirteen years known duration is reported and is probably best classified as auricular tachycardia with A-V block. For a period of two months the auricular rate apparently changed to 136 and later returned to the original rate. Digitalis enhanced the action of carotid sinus stimulation.

The author wishes to express his thanks to Dr. T. Campbell Goodwin, Cooperstown, N. Y., for his aid in furnishing the early history of this case and to Dr. Helen B. Taussig for furnishing the electrocardiograms of 1936-1937.

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REPORT OF A CASE OF VENTRICULAR FIBRILLATION WITH RECOVERY FOLLOWING ACUTE CORONARY OCCLUSION

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VENTRICULAR fibrillation was first described by Ludwig and Hoffa[1] in 1849. While it is most often a terminal event in various forms of cardiac failure, as long ago as 1905, Hering[2] and, in 1906, Deneke and Adams[3] pointed out that the human ventricles may develop transient fibrillation. Schwartz[4,5] and Schwartz and Jezer[6] have shown that periods of unconsciousness in patients with A-V dissociation are associated with transient seizures of ventricular fibrillation more commonly than had been suspected. Theories as to the nature and mechanism of this arrhythmia have been discussed by Wiggers,[7] and the clinical and electrocardiographic manifestations in the syncopal seizures have been well described by Schwartz and Jezer.[6]

That this arrhythmia may follow acute closure of a coronary artery was shown experimentally by Cohnheim and Schulthess-Rechberg[8] in 1881 and by Porter[9] in 1894. In man one of the most common causes of ventricular fibrillation is sudden occlusion of a coronary vessel (usually thrombosis).[7] Even though in such cases it is usually fatal,[7,10,11] that recovery may occur is evidenced by the case reported by Zimdahl and Fulton,[12] in which the patient suffered from fifteen seizures of unconsciousness during a period of eight hours. Electrocardiographic tracings showed the attacks to be transient ventricular fibrillation and confirmed the diagnosis of acute myocardial infarction.

While the opportunity to obtain electrocardiographic tracings during an attack of ventricular fibrillation in a patient with multiple seizures is evident, the chances of securing such a tracing when the patient has only one or two such attacks with recovery is very small. In view of the latter event and the rarity of such reports in the literature with recovery following coronary occlusion, it was thought worthwhile to report the following case.

CASE REPORT

A fifty-eight-year-old white man, who had enjoyed good health previously, developed a sensation of substernal heaviness while playing golf at 10:30 A. M. on July 24, 1948. The symptom was not severe and the patient attributed it to indigestion due to pancakes he had eaten for breakfast. Exertion had no appreciable effect on the discomfort and he continued with the golf game. About one hour and ten minutes later, just after he had made a good drive, the discomfort suddenly became much more severe. Symptoms of shock appeared and he was forced to lie down. The pain at this time was described as a crushing sensation, which began in the substernal region and was felt in the throat, both arms and wrists. He was helped into an automobile and conveyed to his room at the Country Club where he was seen by one of us (F.D.D.) twenty minutes later.

His past history is of interest because of one unexplained attack of syncope about two years prior to the seizure just described.

Examination revealed a well-developed and well-nourished middle-aged man in obvious distress. The skin was cold and clammy. The pulse rate was 100 and the blood pressure 80/60. The heart sounds were distant and soft, with a reduplicated first sound. The patient was given 100 mg. of Demerol intravenously and carried by ambulance to the Martha Jefferson Hospital.

His condition on admission showed little or no change from that of the previous examination. Relief of pain followed the administration of Pantopon and atropine. Three hours after admission to the hospital, when one of us (R.G.M.) entered the patient's room in order to obtain an electrocardiogram, the patient appeared comfortable, alert, cooperative, and made several casual remarks during the time the electrodes were being applied to his limbs. When the tracing for

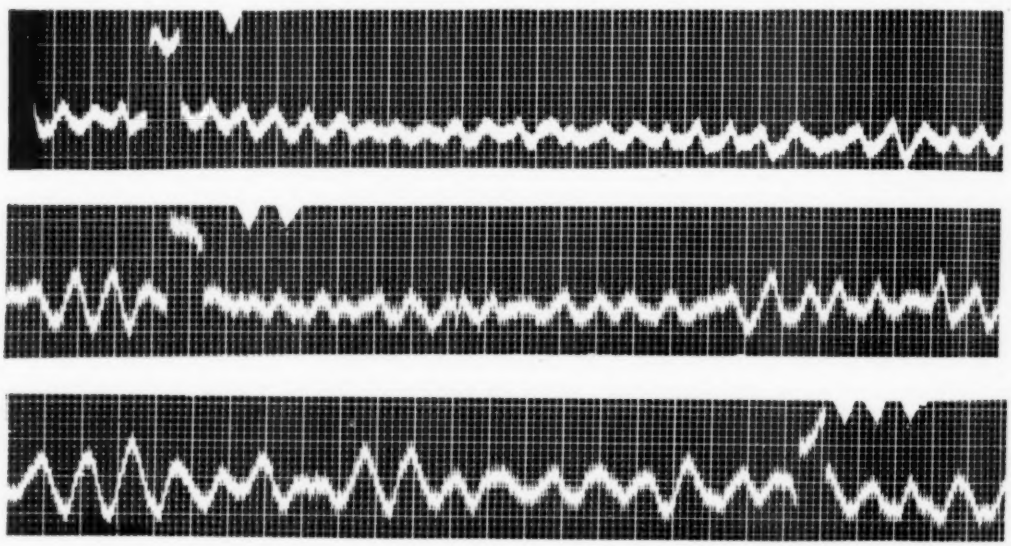

Fig. 1.—Ventricular fibrillation is demonstrated in the irregular ventricular oscillations, with periodic waxing and waning, which vary in height, width, shape, and form. Their frequency is from 150 to 210 per minute.

Lead I was started, it was noted that the oscillations of the beam were very unusual in appearance. During the process of taking Lead II the patient suddenly made several convulsive movements, lapsed into unconsciousness, became pulseless, ceased breathing, and appeared ashen-gray in color. Only by seeing the irregular vibrations of the cardiograph beam, was it determined that the heart was still beating. Adrenalin and caffeine sodiobenzoate were administered immediately and artificial respiration instituted. At periodic intervals during the syncopal attack, electrocardiographic tracings were obtained. In a few minutes the radial pulse became palpable and the patient began to breathe again. Normal color returned to his skin and consciousness was regained. However, he appeared dazed and disoriented for about ten minutes after recovery. It was estimated that the duration of the seizure was approximately four and one-half minutes.

The electrocardiogram demonstrated that the syncopal attack was associated with ventricular fibrillation, which was already in progress when the tracing was started (Figs. 1 and 2). Another electrocardiogram obtained about five minutes following recovery from the period of unconsciousness showed changes consistent with those of a recent acute posterior myocardial infarction (Fig. 3).

The remainder of his stay in the hospital was uneventful. From the second to the ninth hospital day he had an elevation of temperature ranging from 100° to 101.6° Fahrenheit. There

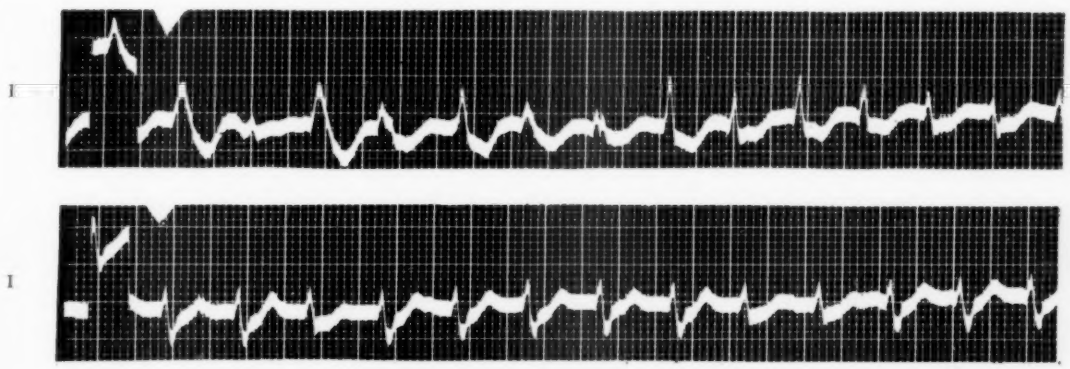

Fig. 2.—During the recovery phase aberrantly conducted impulses are demonstrated. At first the beats are from multiple foci and then in regular rhythm. Their prolonged duration is indicative of bundle branch block.

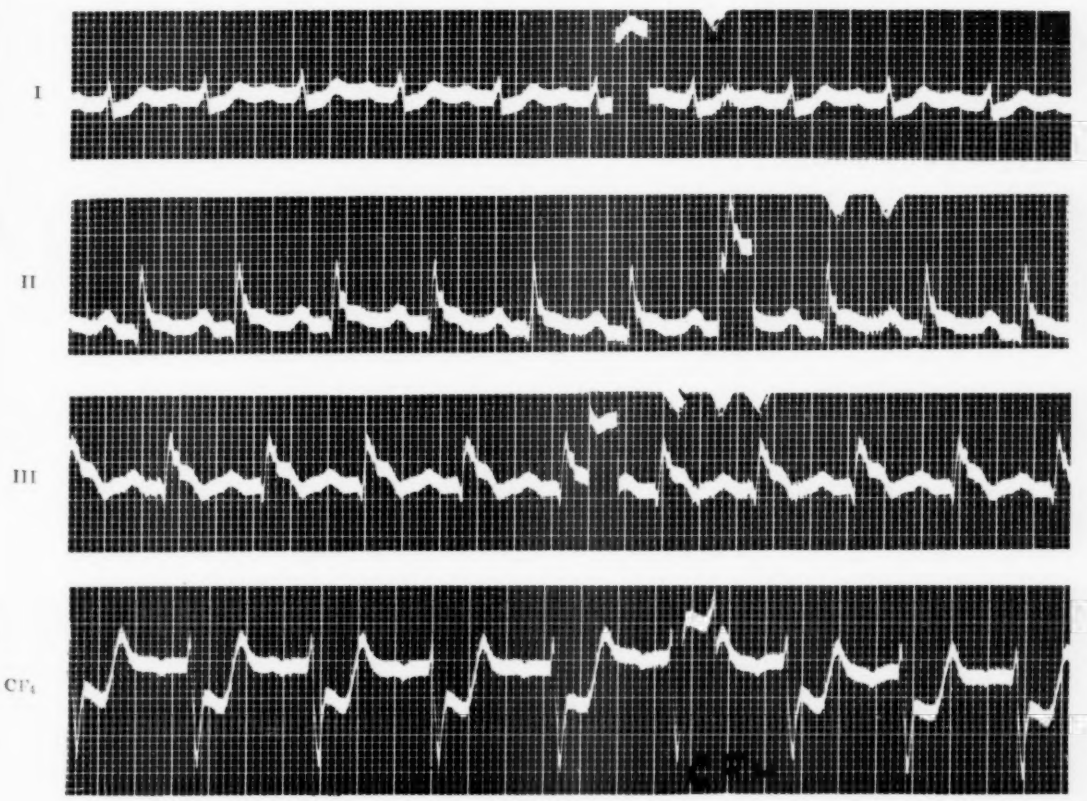

Fig. 3.—The elevated RS-T segments in Leads II and III with inverted T waves in Lead III and marked depression of the RS-T segments in Lead CF_4 are consistent with a recent acute posterior myocardial infarction.

was a transient leucocytosis during this period as well as an increase in the sedimentation rate. The patient was kept in bed and mild sedation in the form of phenobarbital was prescribed. During this time quinidine and Dicumarol were given and the prothrombin time was determined daily. No further ventricular fibrillation occurred on a quinidine ration of 18 grains daily in 3-grain doses for thirty consecutive days. At the end of four weeks he was allowed to get up an increasing length of time each day, and was discharged, ambulatory and asymptomatic, on the thirty-fourth hospital day.

SUMMARY

An attack of ventricular fibrillation is presented. This was verified by an electrocardiographic tracing, coincidentally made during the seizure which followed an acute coronary occlusion. Recovery occurred.

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RUPTURE OF AORTIC ANEURYSM INTO THE SUPERIOR VENA CAVA

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RUPTURE of an aortic aneurysm into the superior vena cava is of rare occurrence; only 102 have been reported to date. The ante-mortem diagnosis is made rather infrequently, either because the clinician is not aware of the syndrome, or because he has discarded the possibility in favor of a statistically more probable diagnosis. However, the diagnosis can and should be made.

Since the first report of a case by Beevor,[1] in 1833, there have been three comprehensive reviews of the case reports: Pepper and Griffith,[2] in 1890, Shennan,[3] in 1925, and Armstrong and associates,[4] in 1939. Pepper and Griffith laid down diagnostic criteria which still stand, fifty-eight years later. Both Shennan and Armstrong included bibliographies listing the known instances, but neither critically excluded reports that did not fit the pathological and anatomical criteria. Some of the cases previously reported had no clinical histories;[1,5] others were not true cases.[6-14] Two were reported twice.[15,16] Since Armstrong's report, twelve cases[17-27] have been reported.

Including the two cases reported at this time, there have been 104 cases, the reports of eighty-three of which were studied by the author. Twenty-one were not reviewed, fifteen could not be found, and for six there was no available translation.

CASE REPORTS

CASE 1.—On July 15, 1945, L. C., a white Italian man, aged 68 years, was admitted (walking) to the Jewish Hospital. The patient stated he had been well until July 13, 1945. On the evening of July 13 he had several drinks. At about 10 P. M. he complained of having a "funny feeling in his head." It was noticed that the patient's face had a reddish-blue color. He had only slight difficulty in breathing and had no pain. On awakening the following morning he complained that his head and eyes felt swollen and that he had a dizzy headache. He attempted to go to work that morning (July 14), but after arriving at work he was unable to continue because of the dizzy sensation. It was known that the patient had been inadequately treated for syphilis.

The essential physical findings were: temperature 97.5 °F. (by mouth); pulse rate 100; respiration rate 40 per minute. The blood pressure was 165/55 in the right arm, with the patient sitting. The patient was well developed, well nourished, and obese. He was sitting up in bed, was rational, and had labored, rapid breathing. His entire face and neck appeared swollen and the veins of the forehead were very prominent. A marked reddish cyanosis of the head, face, shoulders, upper extremities, and upper part of the thorax gave a startling appearance. The skin was cold and clammy over these areas. The remainder of the body had a normal pink color, was warm, and the skin was dry. The veins of the neck were engorged; the trachea was slightly deviated to the

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right. The thorax was moderately emphysematous. The lungs expanded fairly well, the percussion note being impaired over the right upper lobe anteriorly, with bronchovesicular breathing heard over this area. The remainder of the lung fields was clear.

The heart was slightly enlarged to the left of the midclavicular line in the fifth intercostal space. Retrosternal dullness was increased to about 11 cm. (mostly to the right). There was a loud systolic murmur heard over the entire precordium, with a systolic and diastolic murmur heard over the aortic area. A capillary pulse was present. There was no definite Corrigan's pulse. The radial pulse was weak.

Fig. 1.—Heart of Patient L. C. (Case 1). The arrow is in the perforation from the superior vena caval side.

The abdomen had active pulsations, felt widely in the epigastrium. The liver, spleen, and kidneys were not palpable. The extremities were symmetrical and well developed and without edema. The reflexes were physiological. On admission to the hospital, nasal oxygen was started and the patient was given 1/32 grains Dilaudid because of extreme restlessness.

X-ray examination, made with the aid of the portable apparatus, showed an aortic aneurysm, bulging toward the right apex. Additional laboratory work was not undertaken because of the rapid downhill course of the patient. A diagnosis of rupture of an aortic aneurysm into the superior vena cava was made before death.

The autopsy was performed about three hours after death. The body was that of a heavy-set, well developed white man 68 years of age. The skin of the face, neck, thorax, and upper extremities was deeply cyanotic. On opening the thoracic cage a large mass was seen superior to the heart. It was tightly attached to the thoracic wall and could be separated only with difficulty. The

heart weighed 300 grams. On opening the heart the endocardium was found to be smooth, the valves intact and delicate, and the muscle an even brown color. About 3 cm. above the aortic valve there was an outpouching of the aortic wall measuring 10 cm. in diameter. The wall was tough and contained flattened, grayish-pink, thrombotic material tightly attached to the wall, and a large mass of post-mortem clot. In the posterior wall of the aneurysm there was a narrow tear 0.5 cm. in length. A probe inserted into the latter came out in the lumen of the superior vena cava (Fig. 1). The intima showed a number of yellow, raised plaques, which increased in number and intensity in the descending aorta and below the diaphragm. Some of these lesions were ulcerated and showed small deposits of clotted material. The descending aorta, as well as the thoracic aorta, showed shallow constrictions of the intima, typical of tree barking. The orifices of the coronaries were constricted, but the lumina were patent. There was no pleural effusion. The lungs showed congestion, as did the liver and brain.

Microscopic sections of the aorta revealed vascularization of the media and perivascular infiltration around the vasa vasorum in the adventitia. The intima of some of the latter vessels was thickened. The intima of the aorta showed deposits of hyaline and cholesterol.

CASE 2.—The patient, a 57-year-old white man, was admitted ambulant to the hospital on Oct. 9, 1920. He complained of pain in his right clavicle and rapid increase in the circumference of his neck. For a year prior to admission he had had sharp retrosternal pain, which occurred while lying down but was relieved when he sat up in bed. The pain would last about five minutes and would recur at irregular intervals varying from one-half hour to several days. One evening, about two and a half months prior to admission, the pain became very severe, sharp, cutting in character, and radiated to the left of the nipple line. The following morning the patient awoke with pain in the right clavicle, the pain on the left side of the nipple line having disappeared. However, the face, neck, and chest were swollen, so that the patient could hardly see. The swelling subsided slightly and became harder. The patient stated that he had received nine intramuscular injections of what he thought was mercury during the previous two and one-half months. There was some complaint of dyspnea and vertigo on occasions. The patient stated that he had had a chancre at the age of 17 years.

Physical examination revealed a well-nourished man of peculiar proportions. His head, neck, and upper extremities impressed one as those of a man of 180 pounds, while the lower extremities appeared to be those of a man of 120 pounds. The skin of the face, neck, and upper extremities was reddened and cyanotic and there was pitting on pressure, more so on the right than on the left (Fig. 2). The thoracic wall was thickened, the skin showing numerous dark-red dilated veins, some thrombotic, both anteriorly and posteriorly, with an attempt at communication between the superficial thoracic and abdominal veins. Over the chest the right infraclavicular area was slightly more prominent than the left and there was a barely palpable fine thrill. The apex beat was in the fifth intercostal space. Over the prominent area, to the right, there was dullness reaching as far down as the second intercostal space, extending to the apex of the lung and continuous on the left with the retrosternal and cardiac dullness, and with dullness extending as a band below the left clavicle, halfway toward the shoulder. Posteriorly there was distinctly diminished resonance on both sides (more marked on the right) in the supraspinous regions. There was no evident fluid in the pleura. Breath sounds were clear and slightly higher pitched on the right than on the left; at an area about the right scapular angle they possessed an amphoric quality. Above the spines of the scapulae breath and voice sounds were feeble. Breath sounds were feeble over the anterior part of the chest, markedly so on the right. A soft, blowing systolic murmur was heard over the precordium, its greatest intensity over the right infraclavicular region. The pulses were apparently equal in volume. There was a diastolic, blowing murmur over the aortic area. The liver was not enlarged; the spleen was palpable. The electrocardiogram on October 10 revealed a normal curve, and on November 12, left ventricular preponderance, sinus acceleration, and "myocarditis." The urine was normal. The Wassermann reaction was +4. The red count, differential count, and hemoglobin values were normal.

Within a week after admission the patient became increasingly dyspneic, began to cough up blood-streaked sputum, and required morphine so that he could rest. An attempt to digitalize the patient failed to relieve his symptoms. The initial diagnosis was thrombosis of the superior vena cava, due to aneurysm of the aorta. The patient was further treated by bleeding, but became ncreasingly dyspneic, orthopneic, edematous, and irrational and expired on Nov. 26, 1920.

Only a partial autopsy was performed and this was limited to the thorax. The lungs were edematous. The heart was pushed downward and to the left, so that the long axis formed an angle of no more than 20 per cent with the horizontal. The valves showed nothing abnormal. The myocardium was slightly brownish and the coronary vessels were markedly sclerotic. There was no note as to the size of the heart. The aorta showed dilatation from just above the coronary

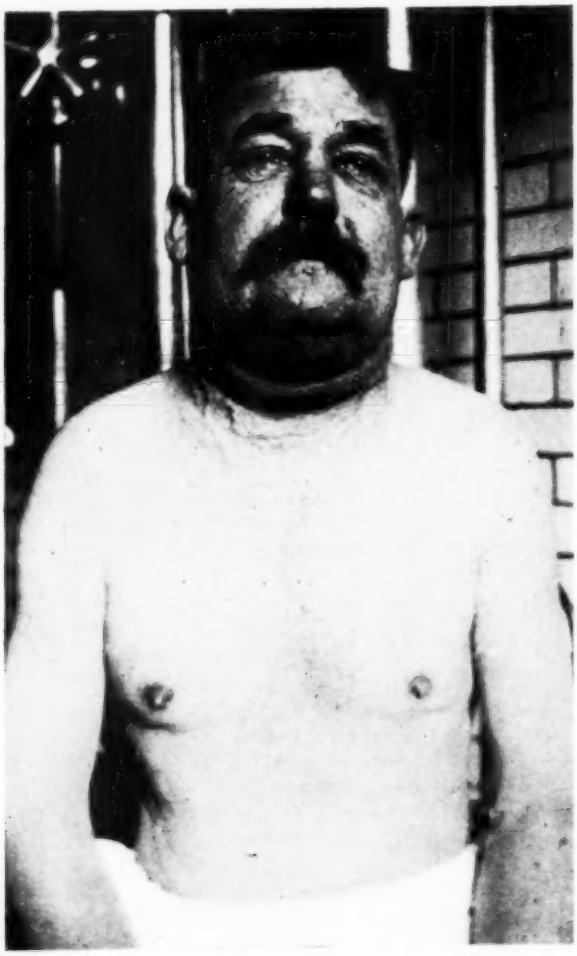

Fig. 2.—The patient in Case 2. Note the typical swelling of the face and neck and the normal-appearing lower thorax as compared to the face and neck.

sinuses throughout the arch and extending to the descending aorta. This was most marked where the ascending aorta and arch joined. Numerous atheromatous plaques were present in the ascending portion. In the ascending portion, towards the right side, an aneurysm was present, about 3 cm. by 1.5 centimeters. This impinged upon the superior vena cava. Just above the aneurysm and the pouch formed by it there was an opening between the superior vena cava and the aorta, 0.5 cm. in diameter. The vena cava was markedly compressed, just before it entered the auricle, by the bulging of the aneurysm. No histological sections were reported.

DISCUSSION

The frequency of rupture of the thoracic aorta varies according to the reports reviewed. The combined figures of Nicholson[28] and Delp and Maxwell[29]

were 52.1 per cent of 304 reports of aortic aneurysm, while those of Boyd[30] and Lemann[31] were 25.5 per cent of 1,249 reports. Of 592 reports of ruptured aortas that Lemann reviewed, 5.2 per cent ruptured into the superior vena cava. Nicholson reviewed 23,239 autopsy reports and found 219 (.09 per cent) thoracic aneurysms. Of these, 50.5 per cent ruptured into some adjacent thoracic space or vessel. The commonest site into which the rupture took place was the right or left pleural cavity (36.4 per cent); in 18.1 per cent it was into the esophagus; in 12.7 per cent into the right or left bronchus; in 10 per cent into the trachea; and also in 10 per cent into the pericordium. It appears that the most frequent rupture took place into the regions with which the aorta had the greatest surface area contact.

Because the ascending and transverse aorta is in close proximity to the pulmonary artery and the superior vena cava, it is difficult to understand the low incidence of rupture into these vessels. On an anatomical basis, the fact that the vessels are relatively short and are mobile rather than fixed may account for the relative infrequency of penetration. The possibility that the clinician has overlooked the significance of the symptoms and no post-mortem examination was obtained may account for a few unreported cases. Boyd[30] felt that aneurysms of the ascending aorta were more commonly on the anterior and right side of the vessel rather than on the posterior and left side. This might account for the slightly fewer number of pulmonary artery arteriovenous aneurysms, but not for the lack of additional ruptures into the superior vena cava.

ANALYSIS OF DATA

Of the eighty-three reports reviewed, in two there were only pathology reports,[1,5] and in three a clinical report but no autopsy record;[22-24] consequently, in some instances the figures are based on eighty-one reports, while in others they are based on eighty.

Age and Sex.—Of the eighty-three ruptures, seventy-three occurred in men and ten in women. Of these patients, 41.5 per cent were between 41 and 50 years of age and 32.2 per cent were between 51 and 60 years of age; thus 73.7 per cent of the patients were between the age of 40 and 60 years. The earliest cases were in two men in their twenties. No case was reported in an individual over 70 years of age.

Cause of Rupture and Method of Onset (Eighty-one Cases).—In 61 per cent of the patients, perforation occurred during ordinary routine, e.g., walking, sleeping, and bending over. Only 24.2 per cent of the ruptures occurred during unusual physical activity or violent emotional disturbance. In 14.8 per cent no cause could be determined. In 76.5 per cent of the patients the onset was sudden, and if the 11 per cent in whom it was indefinitely sudden is added, 87.5 per cent of the perforations can be stated to have occurred abruptly. In 12.5 per cent of the patients the onset was either not mentioned or occurred gradually.

Symptoms (Eighty-one Cases).—In 100 per cent of the analyzed patients there was cyanosis and edema involving part or all of the upper extremities, face, neck, and chest. Dyspnea occurred as the next commonest symptom in 75.8 per cent of the patients. Neck and chest discomfort, described as suffocating,

choking, strangling, or constricting, occurred in 43.3 per cent of the patients. Dysphagia and feeling of faintness occurred in 18.1 per cent, and cough in 16.9 per cent. Other complaints, such as headache, vertigo, hoarseness, diplopia, and unconsciousness were present in a small number of subjects. The swelling extended from the base of the chest upward in 63.5 per cent of the patients, upward from the level of the second to third rib anteriorly in 34.1 per cent, and the face only in 2.4 per cent. Frequently dilated veins made the line of demarcation. The neck was often described as being so swollen that it appeared as if the patient had a horse collar around him.

Physical Findings (*Eighty-one Cases*).—One of the most characteristic findings was a continuous or double murmur heard in the second right intercostal space in 62.5 per cent of the patients. Usually, the maximum intensity was found in the center of an area dull to percussion and corresponding to the site of the aneurysm. The thrill, although found in only 23.1 per cent of the subjects, was generally located over the area where the murmur was heard best. When the murmur was continuous it generally had a systolic accentuation and a decrescendo in diastole. Many described separate systolic and diastolic components more in keeping with an aortic regurgitation. When the murmur was not continuous it was described as "harsh," "rasping," "buzzing," "booming," "swishing," "churning," and "blowing." A systolic murmur alone was heard in 24.2 per cent of the patients, no murmur being heard in 8.5 per cent. In a single patient only a diastolic murmur was described.

Analysis of the character of the pulse proved of little value, since too frequently no remark was made either about the pulse rate or its characteristics. In only six patients was a definite Corrigan's pulse described, while in eleven there was variation in pulses of the upper extremities which was probably due to the location of the aneurysm. Pulse rate analysis was of no value. A widening of the pulse pressure greater than 50 mm. of mercury was present in eleven of the twenty patients whose blood pressure readings were recorded. Blood pressure readings in the lower extremities were infrequently made.

Syphilis and Arteriosclerosis (*Eighty Cases*).—Only in twenty-eight reports was there no remark as to the absence or presence of syphilis. Report of positive serologic reactions post mortem, clinical history, and presumptive evidence (occupation, intemperate habits) showed that many of the patients had had syphilis. In most of the reports made since the advent of the serological test for syphilis positive serologic reactions were given. Arteriosclerosis was present in 50 per cent of the patients. This correlates well with the ages of the patients and also with the observation that arteriosclerosis is commonly present in association with syphilis of the aorta. Frequently, no remark was made in the charts as to its absence or presence.

Pathological Findings (*Eighty Cases*).—The heart was found to be hypertrophied in 40.5 per cent of the patients, normal in 43 per cent, and not mentioned in 16.5 per cent. The aortic valves were normal in 55.5 per cent, abnormal in 19.8 per cent, and not mentioned in 24.7 per cent. The unusually high normal values tend to substantiate the theory that the murmurs, thrills, and signs

ascribed to aortic insufficiency were most probably due to the arteriovenous fistula.

Pleural effusions were present in 45.5 per cent of the patients and in the majority of these (74.9 per cent) were bilateral. These were probably late in developing and were due to interference with the vena azygos major. The back pressure depended more on the position and extent of compression of the superior vena cava than on the position of the perforation relative to the opening of the azygos.

An attempt was made to analyze the point of perforation, number of perforations, and the site of the aneurysm relative to the superior vena cava. Only generalizations may be made about these points, namely, (1) the size of the perforation appeared to influence the intensity of the murmur; (2) most of the aneurysms were present in the ascending aorta; (3) most of the perforations were single, only ten being double and one triple; (4) if the perforation was above the vena azygos, edema and cyanosis appeared to be limited primarily to the head, neck, and upper extremities, while if it occurred opposite or below the vena azygos, the walls of the thorax became edematous and cyanotic and hydrothorax was more prone to occur. This has been confirmed experimentally.[35] The point of perforation was opposite or below the point of entrance of the vena azygos into the superior vena cava in 38.5 per cent of the patients.

Prognosis.—The length of survival is not long. Within the first two months following rupture 70.9 per cent of the subjects died; 29.1 per cent managed to live for periods lasting up to as long as twenty-one months. Three patients were living at the time of report, and no additional report was made.

Diagnosis.—The correct diagnosis was made on 48 per cent of the patients, the majority since 1900. Mayne,[26] in 1846, made the first ante-mortem diagnosis.

PHYSIOLOGY

In 1757, Hunter[37] first described the essential feature of this condition as a fistula between an artery and a vein. Since then there have been numerous observations, both clinical and experimental, and Holman's[38] monograph is probably the best to date.

With the sudden establishment of a vascular short circuit there are several readjustments. There is a fall in systolic and diastolic blood pressure, with an accompanying increase in pulse rate and cardiac output, and rise in venous pressure proximal and distal to the fistula. If the patient survives, further changes take place, namely, the development of an extensive collateral circulation, with tortuous and thickened veins, an increase in blood volume, the return of systolic pressure to its original height, but the diastolic pressure remains low and the heart becomes dilated and hypertrophied. If the fistula is closed, both the immediate and later changes reverse.

An attempt will be made to explain the signs and symptoms on the basis of the disturbed physiology.

Murmur.—In the majority of the reports reviewed (90 per cent) a murmur of some kind was noted in the second right intercostal space. Of this group of patients 24.2 per cent had only a systolic murmur; only one had a simple diastolic murmur, but the remaining had either the characteristic continuous murmur or a

double murmur. The original continuous murmur was described by Thurnam[39], who in turn refers to *Diseases of the Heart* by Dr. James Hope.[40] In the latter book, on page 108, there is found the first description of the "Continuous murmur, augmented in intensity during ventricular systole and diastole, and in both attended with a great degree of purring tremour." Thurnam described the murmur as a "superficial, harsh, and peculiarly intense sawing or blowing sound accompanied by an equally marked purring tremor, heard over the varicose orifice and in the current of the circulation beyond it; this sound is continuous, but is loudest during systole, less loud during diastole, and still less so during the interval."

Since the continuous murmur is not always present, some explanation must be offered. Lamplough[41] suggested three factors that might cause variations: (1) disease of the aortic wall, interfering with the elasticity of the vessels; (2) presence of a large amount of blood clot in the aneurysmal sac; and (3) excessive regurgitation through the cardiac aortic orifice in diseased valves, lowering the pressure in the artery beyond. The last explanation is well worth considering, since in 19.8 per cent of the patients abnormal valves were found at autopsy. There is no satisfactory explanation for the presence of only a systolic murmur, nor for the absence of a murmur in six proved cases.

Thrill.—There was a thrill present in 23.1 per cent of the patients. This was systolic in time and was found over the area of maximum intensity of the murmur. The thrill may be explained by the setting into vibration of the vessel walls as well as the edges of the aneurysmal orifice by the eddies produced at the region of the rent between the aorta and the superior vena cava.

Unfortunately, insufficient data are available from these clinical reports to substantiate the other changes that take place with an arteriovenous aneurysm: (1) fall in systolic and diastolic pressure, with later rise in systolic, and (2) changes in blood volume.

Cyanosis and Edema.—The cyanosis of varying portions of the upper part of the body which developed practically immediately after the rupture of the aneurysm in 100 per cent of the proved cases may be explained by the damming back of the blood entering the superior vena cava.

Murnaghan[17] recently described the results of venous catheterization of the heart in a patient with rupture of an aortic aneurysm into the superior vena cava. Normal pressures in the right auricle and right ventricle are 5 and 25 mm. Hg[42] respectively, and in the superior vena cava the pressure is negative. In Murnaghan's case report it was revealed that the pressure in the right auricle was 3 mm. Hg; in the right ventricle 16 mm. Hg; and in the superior vena cava, 54 mm. of mercury. Consequently, with each systolic thrust the pressure in the superior vena cava is increased and forces the blood back, obstructing its flow towards the heart and resulting in stagnation in the peripheral tissue. As the blood stagnates, the filtration pressure increases and edema results. With the slowing of the blood flow through the small vessels of the skin the blood loses its oxygen and cyanosis develops. This cyanosis is not alternating, for even at the time of diastole with the lowest pressures in the aorta, the pressure is still greater than that normally present in the superior vena cava. It is interesting to note that femoral artery oxygen saturation (85.5 per cent) was lower than expected, leading one to the conclusion that perhaps some venous blood entered into the

aorta. This might occur in patients with a high pulse pressure, resulting in a dynamic imbalance. The obstruction of the flow into the right side of the heart probably accounts partially for the diminished pressures in the right atrium and ventricle. The unusually high oxygen saturation (92 per cent) in the superior vena cava further confirms the arteriovenous fistula.

Dyspnea.—Initial dyspnea was present in 75.5 per cent of the patients. Almost every autopsy disclosed edema of the trachea and larynx. As a rule this produces an oxygen want, due to increased carbon dioxide tension in the blood. There is also a marked venous stasis in the respiratory center and metabolites accumulate which stimulate the center and produce dyspnea.[43,44] Hoarseness and cough may be produced by edema of the upper respiratory passages.

THE SYNDROME

According to the criteria laid down by Pepper and Griffith[2] in 1890, the recognition of an arteriovenous aneurysm of the aorta and superior vena cava may be based on the following principal symptoms and signs: (1) Sudden onset of cyanosis, edema, coldness, and distention of the veins of the upper part of the body, with other evidence of obstruction to the circulation of blood in the tributaries of the superior vena cava. (2) Evidence, from physical examination, of the presence of a tumor in the thorax and the probability that it is aneurysmal. (3) The presence of a murmur characteristic of a communication between an artery and a vein. To this should be added the other phenomena of an arteriovenous aneurysm: (1) collapsing pulse, (2) visible pulsations, (3) capillary pulse, (4) hepatic pulse, (5) blood pressure greater in the legs than in the arms.

SUMMARY

1. There have been reported 104 cases of rupture of an aortic aneurysm into the superior vena cava, including two reported for the first time.

2. The incidence, etiology, pathology, and physiology of rupture of an aortic aneurysm into the superior vena cava are reviewed.

3. The objective findings are due to an arteriovenous aneurysm and are not due to organic disease of the aortic valve.

The author wishes to thank Dr. J. G. Probstein for the use of Case 1, and Dr. J. E. Cook for the use of Case 2.

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SYPHILITIC ANEURYSM OF THE AORTA WITH RUPTURE INTO THE PULMONARY ARTERY

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A PATIENT with syphilitic aneurysm of the aorta with rupture into the pulmonary artery has been observed. The patient survived fourteen months after the onset of his symptoms and after the correct clinical diagnosis was made. During the period of study of this infrequent complication of aortic aneurysm, catheterization of the heart and pulmonary artery was performed and significant results were obtained.

CASE REPORT

J. K., a 40-year-old white man, a truck driver, was admitted to the Medical College of Virginia Hospital on May 15, 1946.

History.—The patient had been well until eight days prior to admission when he awoke with shortness of breath and a cough. Symptoms progressed rapidly and the cough became productive of foamy, slightly bloody sputum. There was no chest pain or edema. The past history was not significant. Four years previously, he had successfully passed a physical examination for life insurance and one given by the Interstate Commerce Commission. The family history revealed no significant data.

Physical Examination.—The patient was well developed and well nourished. He appeared moderately dyspneic, but was otherwise comfortable. His temperature was 101° F.; pulse rate, 112 per minute; respirations, 26 per minute; and blood pressure, 120/50 in both arms. His pupils were equal and reacted normally to light and accommodation. There was no distention of the neck veins. The lungs were clear except for a few medium râles at the left base. By percussion the heart was found to be slightly enlarged to the left; however, there was no widening of supracardiac dullness. The cardiac rhythm was regular. The second aortic sound was barely audible but heart sounds were otherwise normal. In the second and third intercostal spaces to the left of the sternum, there was a loud, coarse systolic murmur followed by a short, blowing diastolic murmur. The systolic murmur was transmitted over the whole precordium and was also audible in the back. The pulse was of "collapsing" quality.

Admission Laboratory Examinations.—Study of the blood showed: erythrocytes, 4,000,000 per c. mm. of blood; hemoglobin, 78 per cent; leucocytes, 19,100 per c. mm.; neutrophiles, 64 per cent; eosinophiles, 2 per cent; lymphocytes, 2 per cent; monocytes, 4 per cent. Urinalysis revealed no abnormality. The reactions to serologic tests for syphilis were positive. The blood sugar was 95 mg. per 100 c.c.; the blood nonprotein nitrogen, 45 mg. per 100 cubic centimeters. Examination of the spinal fluid revealed 31 leucocytes per c. mm. (5 neutrophiles and 26 lymphocytes); total protein, 45 mg. per 100 c.c.; and a strongly positive Wassermann reaction. Electrocardiogram showed no abnormality. Roentgenogram of the chest revealed moderate enlargement of the thoracic aorta, general enlargement of the heart, and moderate pulmonary congestion (Fig. 1,*A*).

Clinical Diagnoses.—The following clinical diagnoses were made: (1) syphilitic aneurysm of the aorta with perforation into the pulmonary artery; (2) congestive heart failure; (3) asymptomatic neurosyphilis; (4) possible bacterial endocarditis superimposed on (1).

From the Medical College of Virginia, Richmond, Va.

Course.—Digitoxin was administered immediately. There was some improvement of the patient's dyspnea and clearing of the pulmonary edema. However, during the thirty-four days of hospitalization the liver became progressively more enlarged. Generally, the patient improved symptomatically. He received a total of 12,000,000 units of penicillin for his generalized syphilitic infection. Temperature ranged between 99° and 102° F. during the first ten days of hospitalization; thereafter fever was absent. Blood pressure was consistently about 120/60. Repeated electrocardiograms revealed no significant changes; stethocardiograms did show evidence of systolic and diastolic components of the murmur originating in the third left intercostal space. Roentgenograms, kymograms, and fluoroscopy of the chest revealed fusiform enlargement of the ascending aorta and of the descending aorta, general enlargement of the heart, and enlargement of the pulmonary conus. After moderate symptomatic improvement, the patient was discharged on June 18, 1946, under treatment with digitoxin.

Second Hospital Admission.—The patient was readmitted to the hospital on June 24, 1946, six days after discharge, complaining of dyspnea, orthopnea, and abdominal pain. On examination it was noted that the cardiac murmurs had changed in that the diastolic component was now louder and more prolonged. The lung bases revealed many medium râles. The liver was moderately enlarged and tender. No edema was present. A roentgenogram of the chest showed progressive enlargement of the heart; on fluoroscopy, a *single* pulsation of the left aortic and pulmonary area was noted by one roentgenologist. Electrocardiogram revealed no essential change. On treatment with diuretics, rapid improvement ensued and the patient was discharged on July 4, 1946.

Third Hospital Admission.—The patient was again admitted to the hospital on July 31, 1946, after four weeks at home. During this period, in spite of vigorous treatment with diuretics, progressively severe heart failure appeared with signs and symptoms of pulmonary congestion and marked enlargement of the liver. Physical examination at this time revealed little change except for a moderate number of râles at both lung bases, greater enlargement of the liver, and

TABLE I. DATA OBTAINED FROM CATHETERIZATION OF THE HEART OF PATIENT J. K., ON SEPTEMBER 9, 1946

	MEAN PRESSURES			
	RIGHT AURICLE	RIGHT VENTRICLE	PULMONARY ARTERY	FEMORAL ARTERY
Normal[1] (mm. Hg)	5	25	25	
Patient J. K. (mm. Hg)	30	30	75	
	ANALYSIS OF OXYGEN IN BLOOD			
	RIGHT AURICLE	RIGHT VENTRICLE	PULMONARY ARTERY	FEMORAL ARTERY
Normal[1] Oxygen Content (volume per cent)	Within 0.5	Within 0.5	Within 0.5	Oxygen capacity, 17.07
Patient J. K. Oxygen Content (volume per cent)	9.66	9.52	13.40	16.04
Oxygen Saturation (per cent)	56.6	55.7	78.5	93.9

Fig. 1.—Roentgenograms (*A*, May 13, 1946; *B*, Aug. 12, 1946; *C*, Oct. 12, 1946) showing progressive enlargement of the heart and progressive prominence of the pulmonic conus.

slight edema of both legs. The murmurs were essentially unchanged. During the next five months of hospitalization, the patient developed chronic congestive heart failure in spite of all treatment. Persistent pleural effusion appeared. The liver became firm and irregular and jaundice was manifest. Catheterization of the right auricle and ventricle and the pulmonary artery was performed (Table I). It was noted that the blood in the pulmonary artery had a significantly higher oxygen content than that in the right ventricle, indicating passage of arterial blood into the pulmonary artery. Pressure within the pulmonary artery was also elevated significantly. On Dec. 12, 1946, the patient was transferred to a convalescent hospital for terminal care.

Fig. 2.—Autopsy specimen of heart showing wrinkling of the intima of the aorta. Thumb extends into the aneurysm and probe passes through the fistulous tract.

Laboratory Examinations During Third Admission.—Urinalysis consistently showed no abnormality. Study of the blood showed no significant change from the original studies. Icterus index was 22 units on Nov. 1, 1946. Bromsulfalein retention (dose, 5 mg. per kilogram of body weight) was 40 per cent on Nov. 11, 1946. Results of other blood chemistry determinations were within normal limits. Repeated electrocardiograms, including unipolar leads, showed no significant changes. Roentgenograms of the chest revealed evidence of progressive pulmonary congestion and cardiac enlargement and increasing prominence in the region of the pulmonic conus (Fig. 1,*A*,*B*, and *C*).

Further Course.—The patient was admitted to the convalescent hospital on Dec. 12, 1946. Chronic congestive heart failure became more and more severe with notable evidence of right-sided failure. The cardiac outline became progressively larger. The systolic murmur remained essentially unchanged; however, the diastolic murmur became inaudible. The electrocardiogram

showed no new abnormalities. The patient became steadily weaker and died on July 1, 1947, fourteen months after the onset of symptoms.

Final Clinical Diagnoses.—Final clinical diagnoses were: (1) syphilitic aneurysm of the ascending aorta with perforation into the pulmonary artery; (2) asymptomatic neurosyphilis; (3) death due to congestive heart failure; (4) cardiac cirrhosis of the liver.

Autopsy Findings.—The autopsy* was performed by Dr. William Grigg. The anatomical diagnoses were: (1) active generalized syphilis; (2) fusiform syphilitic aneurysm of the ascending aorta with rupture into the pulmonary artery; (3) chronic passive congestion; (4) cardiac cirrhosis of the liver.

Fig. 3.—Close-up view of the pulmonary artery showing fistula from aneurysm of aorta (*F*). Note smooth, rounded edges of opening.

The heart weighed 610 grams including a 20-cm. length of aorta and pulmonary artery. The left ventricular wall measured 2.0 cm.; the right ventricular wall, 1.0 cm.; the mitral ring, 8.0 cm.; the tricuspid ring, 12.5 cm.; the pulmonary ring, 7.5 cm.; and the aortic ring, 13.0 centimeters. The epicardium was smooth and glistening. The myocardium was less red than is normal and of flabby consistency throughout. The papillary muscles and trabeculae cordis were hypertrophied. The apex of the right ventricle was rounded. The commissures of all the valves were widened; in addition, the aortic valve leaflets were thickened and contained atheromatous plaques. There was narrowing of the coronary ostia. Longitudinal wrinkling of the intima extended up the aorta and around the coronary ostia. There was a fusiform dilatation of the ascending aorta, measuring 10 cm. in diameter. Five centimeters above the base of the aortic

*Autopsy A-5051.

valves on the left anterolateral aspect of the aneurysm was a bulge 5.0 cm. in diameter which narrowed to an opening 0.7 cm. in diameter connecting the aorta with the pulmonary artery (Figs. 2 and 3). There appeared to be a continuous intima from the former to the latter.

On microscopic examination, atrophy, degeneration, and fibrosis of the myocardium were noted. The intima of the ascending aorta was thickened and hyalinized and numerous round cells were seen around the vasa vasorum in the adventitia and media. At the junction of the fistulous opening and the pulmonary artery, there was a definite line of demarcation at which the elastic tissue stopped. However, the intima appeared to be continuous from the aneurysm, through the fistulous opening, and into the pulmonary artery.

COMMENT AND DISCUSSION

In his study of 4,000 reports of aneurysm of the thoracic aorta, Boyd[2] found that, of all that were complicated by rupture of the aneurysm, in 3.7 per cent there was erosion into the pulmonary artery. Of rupturing aneurysm of the *ascending* aorta, 10.1 per cent perforated into the pulmonary artery; the incidence fell to 1.3 per cent when the aneurysm was located in the *arch*. The reason for this difference becomes obvious on study of the anatomical relations of the aorta and pulmonary artery. In another review of aneurysms of the thoracic aorta, Lehmann[3] found the incidence of rupture into the pulmonary artery to be 3 per cent.

There have been several reports on this complication in the recent literature.[4-10] In 1943, Nicholson[10] reviewed the literature extensively and re-evaluated the signs and symptoms which had been presented in 1839 by Hope.[11] These signs and symptoms were set forth as a specific syndrome in 1941 by one of the authors[9] of this article. Briefly, this syndrome includes many of the following features: (1) severe dyspnea; (2) preponderance of right ventricular failure; (3) a purring systolic and diastolic thrill arising at the pulmonic area; (4) harsh systolic and diastolic murmurs originating in the same area; (5) the peripheral signs of aortic insufficiency; (6) physical and roentgenographic evidence of aneurysm of the ascending aorta; and (7) appearance of right axis deviation in the electrocardiogram. Several observers have noted clinical evidences of chronic right ventricular strain in patients with aortic aneurysms.[4-5] This has resulted from increased pressure within the pulmonary artery caused by the aneurysm either compressing or communicating with the pulmonary artery. Various post-mortem case studies have shown enlargement of the pulmonary artery and unusual hypertrophy and dilatation of the right ventricle.[4,9,10] However, there have been no previous in vivo studies of this syndrome, showing clearly that a communication existed between the aorta and pulmonary artery as indicated by: (1) definite increase of oxygen saturation of pulmonary arterial blood when compared with blood from the right auricle and ventricle; and (2) marked increase of pressure within the pulmonary artery when compared with normal pressure within the right auricle. The data presented in Table I are consistent with no other anatomical lesion than a fistula between the aorta and pulmonary artery. Therefore, the only other pathologic lesion to be differentiated, would be a congenitally patent ductus arteriosus.[1,12]

Theoretically and actually an aneurysm of the ascending or transverse aorta may produce the clinical phenomena of right ventricular strain *before*

rupture into the pulmonary artery. This may occur as a result of sufficient compression of the latter to produce actual partial obstruction of blood flow. Under these circumstances, there would be elevation of the intrapulmonary arterial pressure without increase of the oxygen saturation. When perforation does occur and arterial blood under high pressure passes into the pulmonary artery, the final effect would be elevation of the oxygen saturation of the pulmonary arterial blood. In addition, a second and probably most important new factor then enters into the increase of intrapulmonary arterial pressure. As indicated in a previous article,[9] the effect on pulmonary arterial pressure of blood passing under high pressure from the aorta into the pulmonary artery may well depend upon the direction of flow. As stated, "if a current of blood is shunted from the aorta, a high-pressure tube, into the pulmonary artery, a low-pressure tube, in the direction of the pulmonary current, the pressure proximal to the point of entrance is reduced by the suction effect of the high-tension current. On the other hand, if the current from the aorta enters at a right angle to the pulmonary current or is directed toward the right ventricle, an increase of pressure proximal to the fistula would result." Finally, the factor of the increased amount of blood in the pulmonary circuit, as a result of the abnormal shunt through the arterioarterial fistula, is probably of significance. Thus, three factors enter into the elevation of pulmonary arterial pressure: (1) compression of the pulmonary artery by the aneurysm; (2) the obstructive "water-gate" effect; and (3) increased volume of blood in the pulmonary circuit.

In the reported case, most important information was obtained from catheterization of the right auricle and ventricle and pulmonary artery. Although the physical findings were suggestive enough at the time of the original examination to indicate the correct diagnosis, the subsequent clinical course might have cast some doubt on the pathological lesion present, if cardiac catheterization had not been performed. Many of the phenomena of the typical clinical syndrome were either absent or atypical: (1) at the onset, signs of left ventricular failure were most prominent and persisted although evidence of severe chronic right ventricular failure appeared later; (2) the murmurs were never characteristic; (3) no definite electrocardiographic evidence of right ventricular strain appeared. Nevertheless, it was felt that conclusive evidence of the lesion present was obtained from direct measurements within the cardiac chambers and the pulmonary artery. The one finding which remained unexplained was the persistence of normal axis of the electrocardiogram in spite of prolonged increase of pulmonary intra-arterial pressure; right axis deviation has appeared in all previously reported cases.

SUMMARY AND CONCLUSIONS

1. A patient with syphilitic aneurysm of the ascending aorta with rupture into the pulmonary artery is discussed. The patient survived fourteen months after onset of symptoms.

2. Catheterization of the right auricle and ventricle and the pulmonary artery was performed, with the following findings: increased pressure in the right ventricle and pulmonary artery, and increased oxygen saturation of blood in the pulmonary artery.

3. Catheterization was considered to be an important diagnostic aid for this patient.

We wish to express our gratitude to Dr. Reno Porter and Dr. Carol Goldenthal for their cooperation in the cardiac catheterizations.

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Selected Abstracts

Templeton, J. Y., III, and Gibbon, J. H.: Experimental Reconstruction of Cardiac Valves by Venous and Pericardial Grafts. Ann. Surg. **129**:161 (Feb.), 1949.

Effective surgical therapy of most intracardiac lesions will require operation under direct vision, and, although this is not practical at present in man, it is possible, in the experimental animal, to perform intracardiac operations under direct vision during short periods in which both venae cavae are clamped. Clamping up to nine minutes produced no clinical evidence of permanent neurological damage and the mortality rate was minimal. With the expectation that eventually a practical method of oxygenating large quantities of blood outside the body will permit operation in the open human heart, experiments were undertaken to determine whether grafted tissue could be used to replace a portion of a cardiac valve. The authors give a brief review of the literature on procedures used in intracardiac operations which have been performed without interrupting the circulation, as well as other studies in which the circulation was interrupted and intracardiac operations were performed under direct vision.

A description of the technique used is presented in detail. In 19 dogs, a cusp of the tricuspid valve was replaced by a graft of vein or pericardium sutured in position under direct vision. Seven of these dogs survived in apparent good health from three weeks to seven months after operation. Specimens of the grafts obtained at autopsy after 3 weeks were viable and firmly united to the wall of the heart. In five control animals, a portion of the tricuspid valve was resected and no graft was used. Postoperatively, these animals had loud murmurs and marked precordial thrills, in contrast to the grafted animals in which there were no thrills and either faint, or no, murmurs. Anatomically and functionally the pericardium appeared to be more suitable than a vein as a source for the graft.

BECK.

Snyderman, R., and Tipping, J. S.: Subacute Bacterial Endocarditis. Am. J. Med. **6**:336 (March), 1949.

An analysis of ten successfully treated patients with subacute bacterial endocarditis is presented. All showed positive blood cultures for a nonhemolytic streptococcus. The group consisted of six female and four male subjects ranging in age from 16 to 61 years. Defects involving the mitral valve were found in five patients, the mitral and aortic valves were involved in four patients, and one patient had a congenital defect believed to be a patent ductus arteriosus. Dental work and extraction of teeth in five patients and acute infection immediately prior to the illness in the other five patients were apparently the precipitating factors of the disease.

Although most of the patients in this series were started on 50,000 units of penicillin given intramuscularly every three hours, in all but one the dosage had to be increased to from 75,000 to 200,000 units every three hours. The total dosage varied from 10,950,000 units to 84,000,000 units. Patients received treatment for at least a two-week period after they had become afebrile. The use of anticoagulants is felt to be unjustified. Any known foci of infection should be removed during the latter part of treatment after the disease has been controlled and blood levels of penicillin are at a maximum. Prevention of the disease may be accomplished in many cases of valvular damage due to rheumatic fever or to a congenital defect by the use of sulfonamide drugs or preferably penicillin before, during, and after removal of foci of infection.

SCHWARTZ.

Mellinkoff, S. M., and Pisciotta, A. V.: Cold Hemagglutination in Peripheral Vascular Disease. Ann. Int. Med. **30**:655 (March), 1949.

A 19-year-old soldier, who had previously tolerated exposure to cold without developing any untoward effects, observed bluish discoloration and numbness in the acral exposed parts of the body while crossing the North Atlantic by boat in 1946. When he debarked, early trophic changes in the hands and feet had made their appearance. Because of these symptoms, he was admitted to an Army hospital where the phenomenon was reproducible in the hand immersed in cold water or in all extremities when the body was chilled. All laboratory studies were negative except for the high titer of auto-hemagglutinins present in a refrigerated blood sample containing serum. This agglutination property was not modified by fever nor by foreign protein injections. The author does not infer that the property of auto-hemagglutination was responsible for the development of the Raynaud syndrome in this case, but suggests that chilling may have produced both a reflex vasoconstriction and an auto-hemagglutination with the later contributing, in part, to the symptomatology. The author also discusses the possible relationship which may exist between the susceptibility to cold auto-hemagglutination and Raynaud's disease in general.

WENDKOS.

Hinshaw, D. B., and Brown, A. F.: Rupture of the Coronary Sinus Following Myocardial Infarction. Arch. Path. **47**:298 (March), 1949.

The authors report the first recorded case of rupture of the coronary sinus as a complication of myocardial infarction. The patient was a 72-year-old man suffering with precordial and left arm pain. Electrocardiography was not mentioned. Autopsy revealed a heart of normal size, with advanced coronary atherosclerosis. The left circumflex artery was completely occluded by a recent thrombus. There was an aneurysm in the upper lateral wall of the left ventricle. The adjacent myocardium was soft and a yellowish-grey. Over this necrotic area was a bloody subepicardial extravasation undergoing early organization. This epicardial hematoma extended up from the infarcted zone into the A-V groove surrounding the coronary sinus, which itself was greatly distended with clotted blood. The sinus in one small area showed a defect in its wall continuous with the adjacent intraepicardial hemorrhage. Microscopic examination showed that the coronary sinus was actually thrombosed and part of this thrombus was laminated.

GOULEY.

Prinzmetal, M., Corday, E., Spritzler, R. J., and Flieg, W.: Radiocardiography and Its Clinical Applications. J. A. M. A. **139**:617 (March), 1949.

Radiocardiography, a procedure still in the experimental stage, is a method of studying the pumping qualities of the heart. It involves the rapid intravenous injection of 0.1 to 0.2 millicurie of radiosodium (Na^{24}), a substance which has a half-life of 14.8 hours and which is rapidly excreted in the urine. By means of a Geiger counter tube which is placed over the precordium of the patient and a special ink-writing attachment, a graphic record of the passage through the heart chambers of the radioactive material and its relative concentration is obtained.

In the normal subject two well-defined waves are noted. The first wave, reading from right to left, is the R wave which represents the passage of the radioactive sodium through the right cardiac chambers. This is connected by a plateau-like transitional area to the L wave which records the passage of the Na^{24} through the large pulmonary veins and the left chambers of the heart. Because of dilution of the Na^{24} during transit through the pulmonary circuit, the L wave is normally of lower amplitude and longer duration than the R wave. The descending limb of the L wave is gradual and prolonged.

In preliminary studies of a number of cardiac conditions, certain findings have been apparent. A widened R wave is produced in the presence of dilatation of the right side of the heart, and a widened L wave is found in cases of isolated left heart dilatation. Because of the slow discharge of blood into the lungs when right-sided dilatation is present, a low wide L wave may be found even when there is no left heart chamber dilatation. When cardiac enlargement is demonstrated radiographically, the finding of a normal radiocardiographic tracing would seem to indicate that the cardiac enlargement is due to concentric hypertrophy rather than to chamber dilatation and

incomplete emptying. In cases of right-to-left shunt, there is an absence of the normal transition area between the R and L waves and the L wave is abnormally enlarged. The radiocardiogram was of value in differentiating some cases of heart disease from disorders simulating myocardial insufficiency. Comparative tracings, made after the intravenous injection of radiosodium into the femoral vein and the antecubital vein, are suggested as an aid in the diagnosis of superior and inferior caval obstruction.

HANNO.

Plotz, M.: Possible Hazards of High Fat Diets in Coronary Disease: J. A. M. A. **139**:623 (March), 1949.

Plotz reports a series of twenty-seven patients with pre-existing coronary artery disease who were placed on high fat diets for the treatment of peptic ulcer (twenty-six cases) or for the purpose of gaining (one case). In ten cases death occurred in several months; the six cases which came to necropsy showed myocardial infarction and coronary atheromatosis. The blood cholesterol was determined in three of the ten fatal cases and was over 320 milligrams per cent in two. Of the seventeen nonfatal cases, the anginal pain became more troublesome in twelve patients within one to three months after the institution of the high fat diet and myocardial infarction developed in three.

Because of the probable role of cholesterol in the pathogenesis of atherosclerosis, the author feels that high fat diets in patients with coronary artery disease may be harmful.

HANNO.

Felder, D. A.: Evaluation of the Various Clinical Signs of Thrombophlebitis and Experience in Therapy With Anticoagulants. Surg., Gynec. & Obst. **88**:337 (March), 1949.

Without making any attempt to differentiate between phlebothrombosis and deep thrombophlebitis, the author studied ninety-two patients with venous thrombosis of the lower extremities. Swelling of the limb was the most frequent finding. In most instances it was quite apparent, while in the remainder it could only be determined by measurement of the calf. Tenderness was the symptom next in frequency to swelling. This manifested itself most often as deep calf tenderness, elicited by pressing between the gastrocnemius muscle bellies in the calf, or as calf-squeeze tenderness obtained by gently squeezing the calf from side to side. Homans' sign was positive in only about one-half the patients. In 53 per cent of patients there was an appreciable increase in cutaneous temperature of the affected limb. This was usually accompanied by tenderness and swelling. Cyanosis was an infrequent finding.

With regard to the determination of the level of thrombosis on the basis of the clinical picture, the author was of the opinion that swelling of the thigh and leg and femoral vein tenderness up to the inguinal fold were indications of iliofemoral vein occlusion, while edema limited to the ankle or leg, with no tenderness above the knee, was considered to be due to involvement of the posterior tibial vein. Swelling of the entire extremity with extension into the genitalia was interpreted as indicating thrombosis of the common iliac with occlusion of the hypogastric.

Treatment of the patients with thrombosis was limited for the most part to the use of anticoagulants, bed rest and elevation of the foot of the bed. With Dicumarol the patient's prothrombin time was kept at two to three times normal for fourteen days; during the latter half of this period he was ambulatory. In only fifteen instances was bilateral ligations of the common femoral vein performed. The average period of bed rest after the onset of the phlebitis was ten and one-half days. The author found anticoagulant therapy to be very encouraging since it reduced the incidence of secondary embolism from an expected 30 per cent to 2.17 per cent. He was impressed with the high incidence of thrombophlebitis in patients with cancer and believed that such individuals should have prophylactic postoperative anticoagulant therapy. Paravertebral sympathetic blocks were not considered necessary in the treatment of thrombophlebitis.

ABRAMSON.

Zimmerman, L. M., Miller, D., and Marshall, A. N.: Pulmonary Embolism. Its Incidence, Significance, and Relation to Antecedent Vein Disease. Surg., Gynec. & Obst. **88**:373 (March), 1949.

On the basis of a study of more than 5,000 consecutive and unselected post-mortem examinations, the authors found an incidence of 1 per cent of fatal pulmonary embolism. These were almost always the result of a phlebothrombosis, located generally in the veins of the lower extremities. Two-thirds of the embolic deaths occurred in surgical conditions. However, this was estimated to represent only 1 per 2,000 major operations.

In the light of their findings, the authors concluded that the hazard of pulmonary embolism in the presence of phlebothrombosis can only be obviated by interrupting the venous trunks above the level of the thrombus. Thrombophlebitis, on the other hand, requires the use of anticoagulants to prevent propagation of a bland thrombus, with possible eventual embolism.

ABRAMSON.

Russek, H. I., and Zohman, B. L.: Cerebral Thrombosis Precipitated by Injection of a Mercurial Diuretic. J. A. M. A. **139**:922 (April), 1949.

Three elderly patients with congestive heart failure developed cerebral thrombosis with hemiplegia eight to fourteen hours following an initial injection of 2.0 c.c. of a mercurial diuretic. In each case the drug had provoked a profound diuresis and precipitous fall in blood pressure. The authors advocate the use of smaller initial doses of mercurial diuretics, particularly in elderly individuals, in order to prevent the occurrence of cerebral or coronary thrombosis as a result of too marked a diuresis and fall in blood pressure.

HANNO.

Soloff, L. A., and Zatuchni, J.: Syndrome of Salt Depletion Induced by a Regimen of Sodium Restriction and Sodium Diuresis. J. A. M. A. **139**:1136 (April), 1949.

Reduction of the sodium content of the body by means of a salt-poor diet and the use of mercurial diuretics is a therapeutic measure of established value in the treatment of cases of congestive heart failure and hypertension. Excessive salt depletion, however, may give rise to a number of untoward effects, among which are weakness, anorexia, nausea, vomiting, restlessness, thirst, apathy, mental confusion, fall in blood pressure, increase in pulse rate, shock, and coma. These findings must be differentiated from those resulting from the underlying cardiac disease itself, from the use of digitalis, and from excessive sedation.

The authors present seven cases, including four which terminated in death, which demonstrate the untoward effects of the regimen of sodium restriction and sodium diuresis. The blood urea nitrogen was elevated in all seven cases; the blood chlorides, determined in six cases, were uniformly reduced; and the blood sodium level, determined in only one instance, was diminished.

HANNO.